POST AUTHORIZATION SAFETY STUDY (PASS) PROTOCOL

TITLE: Myozyme (alglucosidase alfa) Safety Information Packet effectiveness evaluation: a health care professional survey

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COMPOUND: Alglucosidase alfa

STUDY NAME: Myozyme SIP EU HCP Survey

The Study is conducted by OXON Epidemiology, hereinafter referred also as the "MAH REPRESENTATIVE".

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Information

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Joint PASS	No
Research question and objectives	The primary objective of this two-wave survey is to assess awareness, readability, usage, usefulness, understanding, knowledge of the management of risks associated with Myozyme and behavioral implementation of key safety information contained in the updated SIP as compared to the previous version of the SIP among HCPs. The secondary objectives are to compare the updated and previous versions of the SIP: - To assess distribution and format of the SIP (paper or electronic) of the updated SIP as compared to the previous version of the SIP among HCPs. - To assess the opinion of HCPs of the appropriateness of the updated SIP as compared to the previous version of the SIP among HCPs. - To identify major determinants of the degree of awareness, readability, usage, usefulness, understanding, knowledge, utility, utilization and behavioral implementation of key safety messages contained in the updated SIP among HCPs. The exploratory objective is to document the reasons for lack of immunological testing with the updated and previous versions of the SIP among HCPs
Country(-ies) of study	France, Germany, Italy, Spain, UK and Poland
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2 LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AP	Analysis Population
CRIM	Cross Reactive Immunologic Material
DMP	Data Management Plan
eDC	electronic data capture
ERT	enzyme replacement therapy
GAA	Acid α-glucosidase
GLM	Generalized Linear Models
GVP	Good Pharmacovigilance Practices
HCP	Health care professional
IAP	Independent Analysis Population
IAR	Infusion associated reaction
MAH	Marketing Authorisation Holder
PAP	Paired Analysis Population
PASS	Post-Authorisation Safety Study
PRAC	Pharmacovigilance Risk Assessment Committee
rhGAA	Recombinant human acid α-glucosidase
RM	Risk Minimisation
RMP	Risk Management Plan
SD	Standard Deviation
SIP	Safety Information Packet
SP	Study Population
Wave 1	Assessment of the previous version of the SIP
Wave 2	Assessment of the updated version of the SIP

3 RESPONSIBLE PARTIES

The execution of this protocol is the responsibility of the following parties:

- Marketing Authorization Holder (MAH)
- MAH representative

3.1 MARKETING AUTHORIZATION HOLDERS

The MAH oversees the MAH representative activities and facilitates Competent Authority submissions.

3.2 MAH REPRESENTATIVE

The MAH representative for this survey is Oxon Epidemiology, a contract research organization delegated to serve as survey coordinating centre for this survey. The MAH representative is responsible for the operational conduct of the survey including recruiting of the participating HCPs throughout the duration of the survey, facilitating data collection and ensuring adherence to local regulations including data privacy. In addition, the MAH representative will draft the study documents, perform the statistical analysis and produce the planned interim and final study reports.

4 ABSTRACT

Title: Myozyme (alglucosidase alfa) Safety Information Packet effectiveness evaluation: a health care professional survey

Version: 3.2

Date: 30 January 2015

Main author: Nawab Qizilbash (OXON Epidemiology)

Rationale and background

The Pharmacovigilance Risk Assessment Committee (PRAC) requested Genzyme, a Sanofi Company to further update the Myozyme Safety Information Packet (SIP) and to propose a study to evaluate the effectiveness of the updated version of the SIP. The updated version of the SIP has been approved by the PRAC and is expected to be implemented in EEA countries where Myozyme is marketed for the treatment of Pompe disease in 3q/4q 2015.

To comply with PRAC requirements, a health care professional survey that assesses the effectiveness of the updated SIP is proposed. The survey will consist of two waves (wave 1 and wave 2) which will be carried out pre- and post-implementation of the updated SIP, at least 18 months apart. The proposed survey is intended to assess whether implementation of the updated SIP has led to increased awareness, usage, usefulness, readability, understanding, clinical knowledge and behavioural implementation of key safety messages compared with the previous version of the SIP. Distribution and opinion of HCPs about the SIP will also be evaluated.

Research question and objectives

Primary objective:

The primary objective of this survey is to assess awareness, readability, usage, usefulness, understanding, knowledge of the management of risks associated with Myozyme and behavioral implementation of key safety information contained in the updated SIP as compared to the previous version of the SIP among HCPs.

Secondary objectives:

The secondary objectives are to compare the updated and previous versions of the SIP:

- To assess distribution and format of the SIP (paper or electronic) of the updated SIP as compared to the previous version of the SIP among HCPs.

- To assess the opinion of HCPs of the appropriateness of the updated SIP as compared to the previous version of the SIP among HCPs.

- To identify major determinants of the degree of awareness, readability, usage, usefulness, understanding, knowledge, utility, utilization and behavioral implementation of key safety messages contained in the updated SIP among HCPs. Determinants include: type of HCP (physician or nurse), role of the HCP in the management of Myozyme, country, age and gender of the HCP, years in the specialty, number of patients for whom Myozyme was prescribed in the previous 12 months, type of practice, type of institution (academic or non-academic) and participation in Pompe Registry.

Exploratory objective:

The exploratory objective is to document the reasons for lack of immunological testing with the updated and previous versions of the SIP among HCPs.

Study design

A two-wave cross-sectional survey (wave 1 and wave 2) will assess awareness, readability, usage, usefulness, understanding, clinical knowledge and behavioral implementation of key safety messages in the previous and updated versions of the SIP, respectively, among HCPs. Therefore, the survey will be carried out pre- and post-implementation of the updated SIP, at least 18 months apart.

Population

The survey will be conducted in France, Germany, Italy, Spain, UK and Poland among HCPs (physicians and nurses) who prescribe Myozyme and/or monitor patients treated with Myozyme.

Inclusion criteria:

HCPs will be invited to participate in the survey provided they have:

- Managed at least one patient in the preceding year on Myozyme for Pompe disease through prescribing, monitoring or administering Myozyme therapy.

Exclusion criteria:

HCPs meeting the following criterion will not be eligible to take part in the survey:

- Current or ex-employee of Genzyme, a Sanofi Company or Sanofi.

Endpoints

The questionnaires (Questionnaire 1 and Questionnaire 2) have been developed following standard survey principles for risk minimisation studies (1). The questionnaires will be comprised of multiple choice and closed-ended questions.

Both questionnaires will have the same structure and will only differ in 4 questions. The structure of the HCP questionnaires is:

A. Acceptance to participate

B. Screening: eligibility, demographics…
C. Questionnaire domains:
   - Questions about the HCP and his/her health care practice
   - Characterisation of the HCP department, service or unit
   - Management and immunology testing during the administration of Myozyme
   - Questions about the Myozyme Safety Information Packet

Primary endpoints:

The updated SIP will be compared to the previous version of the SIP for differences in:

- Percentage of HCPs who are aware of the existence of the SIP
- Usage of the SIP; this will be measured by:
  - the percentage of HCPs for individual responses to the question on the extent to which the SIP has been incorporated into the procedures for the management of Pompe patients in their centres
  - the percentage of HCPs for individual responses to the question on the type of access the HCP has to the SIP
- Levels of HCPs' knowledge and understanding related to the key messages
- Behavior of HCPs around key safety messages
- Levels of readability
- Degree of usefulness

Mean scores for questions grouped by objectives that can be assigned as having a 'correct' response: clinical knowledge, understanding, usage and usefulness.

Secondary endpoints:

The updated SIP will be compared to the previous version of the SIP for differences in proportion of HCPs who have received the SIP.

The updated SIP will be compared to the previous version of the SIP for differences in opinion of HCP.

The updated SIP will be compared to the previous version of the SIP for differences in determinants of response: type of HCP, country, age and gender of HCP, years in specialty, number of patients for whom Myozyme was prescribed in the previous 12 months, type of practice, type of institution (academic or non-academic) and participation in Pompe Registry.

The updated SIP will be compared with the previous SIP for differences in qualitative reasons for lack of immunological testing among HCPs.

Data Sources

The approved version of the questionnaire will be cognitively pretested by HCPs and translated into local languages.

A web-based electronic data capture (eDC) system will be used to collect HCP responses to the questionnaire. The questionnaire will be self-administered (closed-ended questions) and can be completed at the participants' convenience. Participants will not be able to go back and change answers to previous questions. This restriction minimises the likelihood of the respondent searching for answers via the web or other sources. Participants will also not be allowed to access the questionnaire once it has been completed and submitted.

Study size

Due to the rarity of the disease, the number of HCPs as a pool for this survey is limited. The estimation of the sample size is based on the ability to detect differences in the primary endpoints between responses to survey wave 1 (related to the previous version of the SIP) and to survey wave 2 (related to the updated SIP). No information is currently available on the expected values for these primary outcomes. For endpoints measured on a continuous scale from 0 to 10, a sample of 100 physicians and nurses will allow for the detection of a minimum difference of 0.25 points between surveys 1 and 2, with 95% precision and 80% power, using a two-way paired t-test. The 95% confidence intervals around estimates of usefulness, readability or knowledge scores for standard deviations of 1, 2, 3 and 4 points are 0.18, 0.36, 0.53 and 0.71, respectively. A high participation rate of approximately 80% from HCPs is expected due to the rarity of the disease and the high degree of specialization of the HCPs involved, although response rates may vary by country and specialty.

Data analysis

Descriptive analyses: Categorical data will be summarized by counts and percentages. Continuous data will be summarized using number, mean, standard deviation (SD), median, quartiles, minimum and maximum and in the case of non-normally distributed data, median, range and interquartile range.

Primary analyses:

The primary analysis, for each survey, will assess awareness, readability, usage, usefulness, understanding, patient management and behavioral implementation including the degree of immunological testing of key safety information by percentages and mean scores, as it corresponds. To assess the effectiveness of the updated SIP in the primary endpoints described above, comparisons of these endpoints between the two waves of the survey will be made. These comparisons will be done separately for those HCPs who responded to the survey in both waves and for those who only answered in one wave with different statistical techniques. The results will be presented in total and stratified by the following factors: country, HCP type, practice setting, risk minimization (RM) tool users vs. non-users. HCP types will be categorized for analysis within individual countries and across the participating countries as a whole, by grouping the response options to survey questions on HCP type.

Secondary analyses:

Distribution of the SIP: For each survey it will be calculated by:

- The percentage of HCPs who respond that they know the existence of the SIP and have received and have read the SIP
- The percentage of HCPs who have received the SIP by source of information
- The percentage of HCPs who have not received or read the SIP
- The percentage of HCPs who received the SIP after their first prescription or administration of Myozyme
- The percentage of HCPs who received the SIP in the last 18 months

Opinion of HCPs of appropriateness of the SIP: it will be calculated by the percentage of HCPs who scored <3 points, or >6 points to all questions regarding clarity, conciseness, completeness, briefness, necessity and usefulness in each of the questionnaires.

Percentages will be analysed with the appropriate statistical techniques to compare categorical data for related samples and independent samples. The results will be presented in total and stratified by the following factors: country, HCP type, practice setting, RM tool users vs. non-users. HCP types will be categorized for analysis within individual countries and across the participating countries as a whole, by grouping the response options to survey questions on HCP type.

Determinants of response: all primary endpoints will be analysed by subgroups for the study of associations at each survey. Subgroups will be determined by the following variables: type of HCP (physician or nurse), role of the HCP in the management of Myozyme, country, age group, gender of the HCP, years in the specialty, number of patients for whom Myozyme was prescribed in the previous 12 months, type of practice, type of institution (academic or non-academic) and participation in the Pompe Registry.

5 AMENDMENTS AND UPDATES

None

6 MILESTONES

Milestone	Planned date
Cognitive pretesting of the questionnaire	December 2014 to February 2015
Registration in the EU PASS register	February 2015
Start of data collection – wave 1	May 2015
End of data collection – wave 1	July 2015
Interim study report	September 2015
Start of data collection – wave 2	November 2016
End of data collection – wave 2	January 2017
Final report of study results	March 2017

7 RATIONALE AND BACKGROUND

7.1 BACKGROUND

Pompe disease is a rare inherited disorder leading to reduced levels of acid α-glucosidase (GAA), an enzyme that degrades lysosomal glycogen to glucose. GAA deficiency leads to glycogen accumulation and the eventual rupture of lysosomes, resulting in cellular dysfunction in many body tissues, particularly muscle fibres. The disease can appear at birth (the 'infantile-onset' form) but also later in life (the 'late-onset' form). The estimated global incidence of Pompe disease is 1:40,000 (2).

Myozyme® (alglucosidase alfa) indication and administration

Myozyme contains the active ingredient alglucosidase alfa (recombinant human acid α-glucosidase [rhGAA]). Myozyme is indicated for long-term enzyme replacement therapy (ERT) in patients with a confirmed diagnosis of Pompe disease (acid α-glucosidase deficiency), in adults and paediatric patients of all ages. The recommended dosage regimen of alglucosidase alfa is 20 mg/kg of body weight administered once every 2 weeks as an intravenous infusion. Infusions should be administered incrementally. It is recommended that the infusion begin at an initial rate of 1 mg/kg/hr and be gradually increased by 2 mg/kg/hr every 30 minutes if there are no signs of infusion associated reactions until a maximum rate of 7 mg/kg/hr is reached. Myozyme treatment should be supervised by a physician experienced in the management of patients with Pompe disease or other inherited metabolic or neuromuscular diseases (3).

Myozyme safety profile

The last submitted Myozyme Risk Management Plan (RMP version 7.2 dated 05 August 2014) identifies the following important risks:

- Infusion Associated Reactions (IARs) including hypersensitivity and anaphylactic reactions
- Immune-mediated reactions
- Immunogenicity: anti-rhGAA IgG Antibodies, inhibitory antibodies to rhGAA, anti-rhGA IgE antibodies
- Acute cardiorespiratory failure associated with fluid overload

Infusion Associated Reactions (IARs) including hypersensitivity and anaphylactic reactions
An IAR is defined as any adverse event (AE) occurring during the infusion or during the hours following infusion and assessed as potentially causally related to the administration of the product (Myozyme). Related events occurring after the post-infusion period may be considered IARs at

the discretion of the reporter. The exact mechanism for IARs is not fully understood (4,5). In clinical trials, the occurrence of IARs was approximately 50% in infantile-onset patients treated with Myozyme (over a period of 52 weeks) and 28% in late-onset patients (over a period of 18-months) (3). The occurrence of lARs is not unexpected given the clinical presentation of immunogenic responses to recombinant human proteins. While the majority of reactions were assessed as mild to moderate, some were severe. Some patients in clinical trials and in the commercial setting developed anaphylactic shock and/or cardiac arrest during Myozyme infusion that required life-support measures. Reactions generally occurred shortly after initiation of the infusion. Patients presented with a constellation of signs and symptoms, primarily respiratory, cardiovascular, oedematous and/or cutaneous in nature. Additionally, recurrent reactions consisting of flu-like illness or a combination of events such as fever, chills, myalgia, arthralgia, pain, or fatigue occurring post-infusion and lasting usually for a few days, have been observed in some patients treated with Myozyme. Patients who have experienced lARs (and in particular anaphylactic reactions) should be treated with caution when re-administering Myozyme.

Immune-mediated reactions

Severe cutaneous and systemic immune-mediated reactions have been reported in somepatients treated with Myozyme. Reactions are self-limiting and usually develop within 7 to 10 days of antigen infusion, starting with some constitutional flu-like symptoms: fever, myalgia, arthralgia and rash. Clinical recovery is usually apparent after 7 to 28 days. Severe cutaneous reactions, including ulcerative and necrotizing skin lesions, possibly immune-mediated, have been reported with Myozyme. Skin biopsy in one patient demonstrated deposition of anti-rhGAA antibodies in the lesion. Systemic immune-mediated reactions, including possible type III immune complex-mediated reactions, have been observed with Myozyme. These reactions occurred several weeks to 3 years after initiation of Myozyme infusions. Nephrotic syndrome was observed in a few patients with Pompe disease treated with Myozyme and who had high IgG antibody titres (≥ 102,400). In these patients renal biopsy showed immune complex deposition. Patients improved following treatment interruption.

Immunogenicity: anti-rhGAA IgG Antibodies, inhibitory antibodies to rhGAA, anti-rhGA IgE antibodies

In clinical studies, the majority of infantile-onset and late-onset Pompe patients developed IgG antibodies to alglucosidase alfa, generally within 3 months of initiation of treatment (6,7). Similar proportions of patients treated in the commercial setting have developed anti-rhGAA IgG antibodies. A tendency was observed for infantile-onset patients treated with a higher dose (40 mg/kg) of Myozyme to develop higher titres of IgG antibodies and experienced more lARs.

It has been observed that some patients who develop high and sustained IgG antibody titers, including Cross Reactive Immunologic Material (CRIM)-negative patients (patients in whom no endogenous GAA protein was detected by Western blot analysis), may experience reduced

clinical treatment efficacy with Myozyme. The cause of a poor clinical response in these patients is thought to be multi-factorial.

Some patients treated with Myozyme in clinical trials and/or the post marketing setting were tested positive for inhibition of enzyme activity and/or uptake. The clinical relevance of in vitro inhibition is unclear. Patients with positive uptake inhibition generally had higher IgG antibody titres than patients who remained negative for uptake inhibition in infantile-onset and late-onset studies. To date, no relationship between inhibition status and the adverse events has been established. The effects of inhibitory antibody development on the long term safety and efficacy of Myozyme are not fully understood.

Some Myozyme treated patients in clinical trials and the post-marketing setting who were evaluated, tested positive for presence of alglucosidase alfa-specific IgE antibodies, some of whom experienced anaphylaxis.

Testing was typically performed for moderate or severe or recurrent IARs suggestive of hypersensitivity reactions. Skin testing, a more sensitive measure to detect IgE antibodies, was also performed for some patients. All patients made a full recovery from the reactions. Some patients were successfully re-challenged and continued to receive treatment with Myozyme using a slower infusion rate at lower initial doses (in line with desensitisation guidelines) and continued to receive treatment under close clinical supervision. Patients who develop IgE antibodies to alglucosidase alfa appear to be at a higher risk for the occurrence of IARs and/or anaphylactic reactions.

Acute cardiorespiratory failure associated with fluid overload
Infantile patients with underlying cardiac hypertrophy are at risk. Patients with an acute underlying illness at the time of Myozyme infusion may be at greater risk of acute cardiorespiratory failure. A few reports of fluid overload have been received.

Acute cardiorespiratory failure requiring intubation and inotropic support has been observed up to 72 hours after infusion with Myozyme in a few infantile-onset patients with underlying cardiac hypertrophy, possibly associated with fluid overload with intravenous administration of Myozyme.

Myozyme additional Risk Minimisation

As part of the Myozyme RMP, a Safety Information Packet (SIP) has been developed with the aim to serve as an educational resource for treating physicians. Treating physicians may make this material available to other health care professionals (HCPs) involved in the management of the disease as required (i.e. pharmacists, non-specialist physicians, allergists, nurses). The SIP is designed to minimize the aforementioned identified risks associated with Myozyme and contains a description of identified risks, a dosing and administration guide, suggested infusion IAR

management guidelines, adverse event reporting guidelines and immunological testing procedures.

Myozyme Safety Information Packet

In May 2014, the Pharmacovigilance Risk Assessment Committee (PRAC) requested Genzyme to further update the SIP by including the elements listed in Table 1. Additionally, during the update process, which involved the conduction of focus groups and cognitive interviews with HCPs (treating physicians and nurses), other areas for improvement were identified. On 20th November 2014, the PRAC has issued a request for supplementary information to further update the SIP. Once PRAC approval has been received (expected by February 2015), the updated SIP will be implemented in EEA countries where Myozyme is marketed for the treatment of Pompe disease in 3q/4q2015. The Marketing Authorisation Holder (MAH) will agree the country-specific details of the SIP with National Competent Authorities in these countries.

Table 1 Summary of the regulatory requirements and objectives of the SIP update process

Objectives of the SIP update process	
PRAC requirements	- To mention that HCPs are asked to report any suspected adverse reactions via the national reporting system - To include a reminder that all patients are encouraged to enroll in the Pompe patient registry - To add more detailed guidelines about skin testing procedure - To systematically associate the diffusion of the SIP with guidelines for the collection, processing and shipment of samples for testing - To improve the document readability
Areas for improvement identified in the Focus Groups with HCPs (nurses and treating physicians) during the	- The SIP needs to offer practical advice. - Key information should be easily accessible: On a practical level, key information needs to be highlighted in the body of the text in order for users to reach the key data quickly. - The SIP needs to be succinct with bullets points. - Overall the document was too long. As this is aimed at experts in Pompe disease, basic information needs to be removed in order to have an easy-to-use document.
Additional objectives identified by Genzyme	- To make the SIP shorter and clearer, and keep all the content within just one document. - To include a 2 page summary of 'What you need to know' - To include key points in each section. - To include diagrams and practical points. - To rearrange the structure of the SIP in order to improve its readability. - To create awareness of the SIP by the HCP treating Pompe disease. - To develop a for a more user-friendly, electronic version of the SIP
Format of the Updated SIP	Electronic and paper
Structure of the Updated SIP	1. Description of identified risks associated with Myozyme a. Infusion associated reactions including hypersensitivity and anaphylactic reactions

b. Immune-mediated reactions
c. Immunogenicity
d. Risks associated with concomitant immunomodulation
e. Acute cardiorespiratory failure associated with fluid overload

2. Clinical management of identified risks
   a. Pre-infusion stage
   b. Myozyme infusion stage
      i. Recommended infusion rate
      ii. Mild or moderate reactions
      iii. Severe reactions hypersensitivity/anaphylactic reactions including anaphylactic shock and IgE-mediated hypersensitivity reaction
   c. Post-infusion observation
3. Testing
   a. Description
      i. Immunosurveillance program: IgG antibody testing including inhibitory antibodies
      ii. Immunology testing for infusion reactions: IgE, complement activation and serum tryptase testing
      iii. Skin testing
   b. Procedure for testing
4. Pregnancy and breastfeeding
5. Reporting suspected reactions
6. Pompe Registry
7. Appendices
   a. Preparation of Myozyme
   b. Administration of Myozyme
   c. Storage of Myozyme

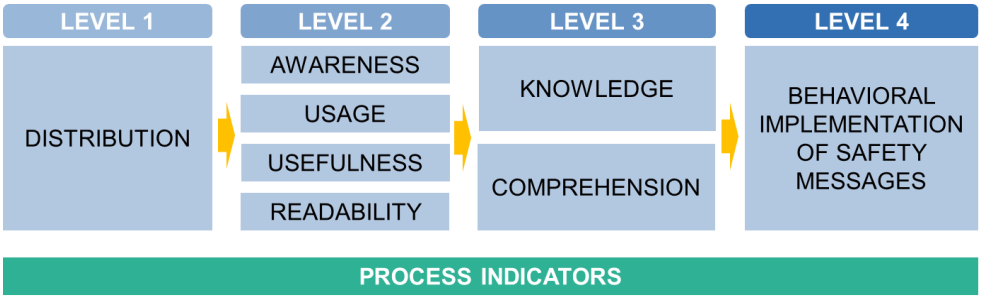
Evaluation of the effectiveness of the updated SIP

The PRAC also requested Genzyme to propose a study to evaluate the effectiveness of the updated version of the SIP, including:

- *Process indicators*: The process itself (i.e. the guide distribution process), the physicians' opinion about the updated guide (readability, content etc.) and their knowledge of the patients' management including immunology testing.
- *Outcome indicators:* to assess the percentage of patients with significant hypersensitivity/ anaphylactic reactions who underwent immunology testing. The evaluation of outcomes will be dealt with elsewhere in another study protocol.

The proposed survey is intended to assess whether implementation of the updated SIP has led to increased awareness, usage, usefulness, readability, understanding, clinical knowledge and behavioural implementation of key safety messages compared with the previous version of the SIP. Distribution, format and opinion of HCPs about the SIP will also be assessed (Figure 1). To this end, a survey will be carried out pre- and post-implementation of the updated SIP.

Figure 1. Components and levels of the evaluation of the Myozyme SIP



This post-authorization safety study (PASS), which consists of a two-wave HCP survey (pre- and post- implementation of the updated SIP), has been designed to meet the requirements of Good Pharmacovigilance Practices (GVP) module VIII: 'Post-authorization safety studies' (8) and module XVI: 'Risk minimization measures - Selection of tools and effectiveness indicators' (1) The timing of this evaluation is at a suitable interval before and after the implementation of the updated SIP in relevant markets, with the previous version of the SIP expected to have been available since Q4 2011 and the updated version of the SIP which is planned to be available from 3q/4q2015. This protocol also takes into account the key elements of survey methodology described in GVP Module XVI (1) in terms of sampling procedures and recruitment strategy; design and administration of the data collection instruments; analytical approach; as well as ethics, privacy, and overall study feasibility.

The results of the survey will be analyzed to assess the effectiveness of the updated SIP in fulfilling the objectives. The results should be interpreted in the context of the evaluation of the effectiveness of the updated SIP which also involves the assessment of clinical outcomes (which will be addressed elsewhere). The survey results will be submitted to PRAC and will also evaluate whether and how further updating the SIP should occur and the need and timing of any further evaluation.

7.2 RATIONALE

To comply with PRAC requirements, a survey that assesses the effectiveness of the updated SIP is proposed. The survey will consist of two waves (wave 1 and wave 2) which will be carried out pre- and post-implementation of the updated SIP.

8 RESEARCH QUESTION AND OBJECTIVES

The research questions are:

- Has implementation of the updated Myozyme SIP for the treatment of patients with Pompe disease as an additional risk minimisation (RM) measure increased: awareness, readability, usage, usefulness, understanding, clinical knowledge and behavioural implementation of key safety messages compared with the previous version of the SIP?
- Has the updated Myozyme SIP been distributed more effectively as compared to the previous version of the SIP?
- What is the opinion of HCPs about the appropriateness of the updated SIP compared to the previous version of the SIP?

8.1 PRIMARY OBJECTIVE

The primary objective of this survey is to assess awareness, readability, usage, usefulness, understanding, knowledge of the management of risks associated with Myozyme and behavioral implementation of key safety information contained in the updated SIP as compared to the previous version of the SIP among HCPs.

8.2 SECONDARY OBJECTIVES

The secondary objectives are:

- To assess distribution and format of the SIP (paper or electronic) of the updated SIP as compared to the previous version of the SIP among HCPs.
- To assess the opinion of HCPs of the appropriateness of the updated SIP as compared to the previous version of the SIP among HCPs.
- To identify major determinants of the degree of awareness, readability, usage, usefulness, understanding, knowledge, utility, utilization and behavioral implementation of key messages contained in the updated SIP among HCPs. Determinants include: type of HCP (physician or nurse), role of the HCP in the management of Myozyme, country, age and gender of the HCP, years in the specialty, number of patients for whom Myozyme was prescribed in the previous 12 months, type of practice, type of institution (academic or non-academic) and participation in the Pompe Registry.

8.3 EXPLORATORY OBJECTIVES

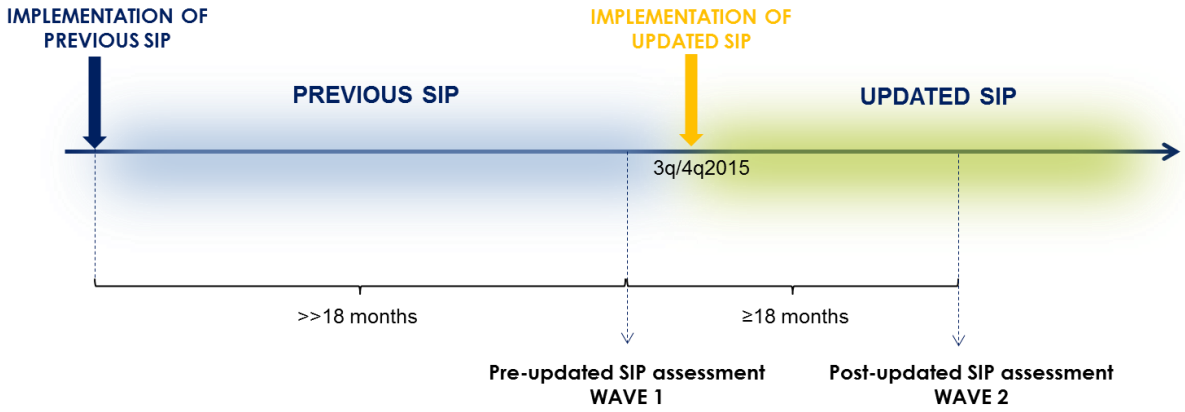
The exploratory objective is to document the reasons for lack of immunological testing with the updated and previous versions of the SIP among HCPs.

9 RESEARCH METHODS

9.1 STUDY DESIGN

This two-wave cross-sectional survey will examine the effectiveness of the SIP used to educate HCPs about the risks associated with Myozyme treatment and immunology testing in patients treated with the drug. The survey will consist of 2 waves (wave 1 and wave 2) and will assess awareness, readability, usage, usefulness, understanding, clinical knowledge and behavioral implementation of key safety messages in the previous and updated versions of the SIP, respectively, among HCPs. Therefore, the surveys will be carried out pre- and post-implementation of the updated SIP, at least 18 months apart. The updated SIP is expected to be implemented in the participating countries in 3q/4q 2015.

Figure 2. Illustration of the study design



9.2 SETTING

The survey will be conducted in the countries with most of the usage of Myozyme in Europe (**Error! Reference source not found.**): France, Germany, Italy, Spain, UK and Poland among HCPs (physicians and nurses) who prescribe Myozyme and/or monitor patients treated with Myozyme.

The participating countries cover approximately 70% (Genzyme data on file) of all Myozyme patients in EEA countries. These countries have been selected to provide a wide range of situations in which to evaluate the SIP in Europe which will serve to reflect the effectiveness of the risk minimisation measure in different types of health care systems: the General Practitioner has a gate-keeper function (UK, Spain and Italy), health insurance which is part of the social security system (Germany) and mixed (France and Poland). In addition, depending on country, different specialties will be involved.

9.2.1 Duration of the study

As depicted in Figure 2, the survey will be conducted at two different time points, before (wave 1) and after (wave 2) the updated SIP has been implemented in each of the participating countries. Wave 1 and wave 2 surveys will be performed at least 18 months apart.

It is planned that the updated SIP will be implemented in 3q/4q2015. However, local versions of the SIP need to be agreed with local national authorities which will dictate when the updated SIP is introduced in each country.

9.2.2 Eligibility criteria

Each HCP should meet all inclusion criteria and none of the exclusion criteria.

9.2.2.1 Inclusion criteria

HCPs will be invited to participate in the survey provided they have:

- Managed at least one patient in the preceding year on Myozyme for Pompe disease through prescribing, monitoring or administering Myozyme therapy.

9.2.2.2 Exclusion criteria

HCPs meeting the following criterion will not be eligible to take part in the survey:

- Current or ex-employee of Genzyme, a Sanofi Company or Sanofi.

9.2.3 Analysis population(s)

Study Populations

The population for each survey will include all HCPs in the participating countries who are involved in the management of Pompe disease patients and have been targeted by the MAH to receive the SIP at the time of conduction of the survey:

- Study Population of survey wave 1
- Study Population of survey wave 2

Analysis Populations

The analysis population for each wave survey will consist of all HCPs fulfilling the eligibility criteria in the study population:

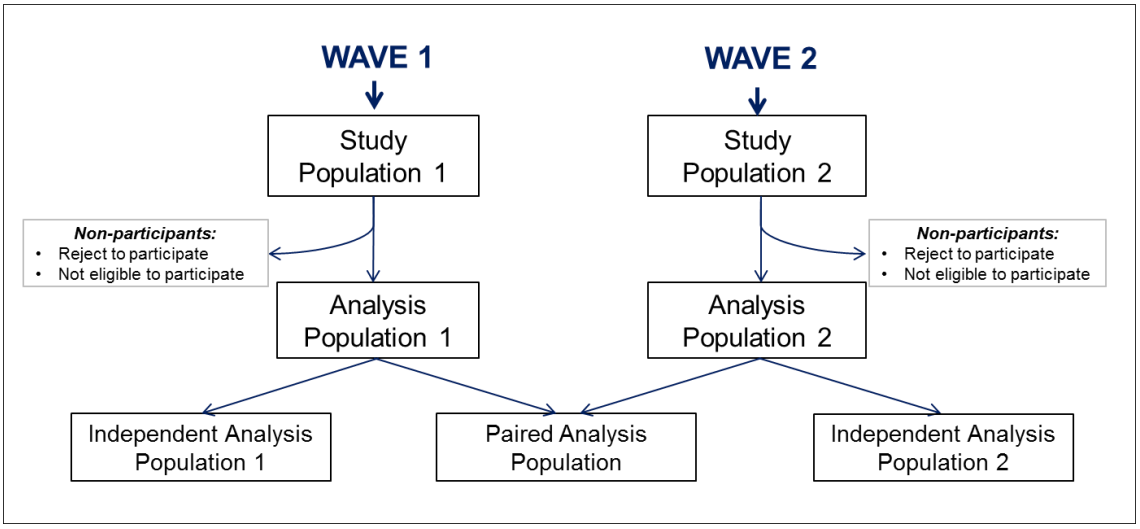
- Analysis Population of survey wave 1
- Analysis Population of survey wave 2

Although the study design responds to an evaluation comparing pre- and post- assessments, and it is likely to include the same HCPs, given the rarity of the disease, Study Populations and Analysis Populations might differ among themselves (Figure 1). HCPs included in survey wave 1 might not participate in wave 2 and vice versa.

For the assessments of longitudinal changes in the primary endpoints (Section 9.7), three analysis sub-populations may be found. These sub-populations will be the Paired Analysis Population and the Independent Analysis Populations of survey wave 1 and survey wave 2. The Paired Analysis Population will be composed of all HCPs who have responded to both survey waves. The Independent Analysis Populations will be composed of those HCP who have only responded to one of the survey waves.

- Analysis Population of survey wave 1
- Analysis Population of survey wave 2
- Paired Analysis Population of survey wave 1 and wave 2

Figure 3. Flow diagram of the analysis populations



9.2.4 Modalities of recruitment

9.2.4.1 Health care professional selection

The survey will involve a variety of HCP specialties, which will depend on country: neurologists, paediatricians, metabolic specialists, neuromuscular specialists, and nurses. As Pompe disease is a rare disease and the number of HCPs who have managed this type of patients is expected to be low, the selection process will aim to target as many HCPs as possible. For each survey wave, Genzyme will provide OXON Epidemiology with a list of centres susceptible to have received the SIP. OXON will retrieve information from various sources on the availability and distribution of physicians involved in the management/monitoring of Pompe disease patients in each centre. OXON will then approach the identified physicians to either invite them to participate in the

survey and/or to propose a nurse within their centre to participate. If a HCP refuses to participate, the next physician in the list will be approached. This procedure will be followed until the desired sample of physicians and nurses per country is obtained.

Based on potential country specific requirements, the recruitment process may be different between countries. HCPs will be identified by a unique identification code. The same selection procedure will be carried out for the two waves of survey. This will allow for the identification of HCPs who have participated in both wave 1 and 2 surveys (identified by their ID).

9.2.4.2 Patient selection

Not applicable

9.3 VARIABLES

Structure of the questionnaires

The questionnaires (Questionnaire 1 and Questionnaire 2) have been developed following standard survey principles for risk minimisation studies (1). The questionnaires will be comprised of multiple choice and close-ended questions.

Both questionnaires will have the same structure and will only differ in 4 questions which will only be shown in Questionnaire 2 (Q5, Q27, Q29 and Q34). The structure of the HCP questionnaires is:

D. Acceptance to participate
E. Screening: eligibility, demographics…
F. Questionnaire domains:
   - Questions about the HCP and his/her healthcare practice
   - Characterisation of the HCP department, service or unit
   - Management and immunology testing during the administration of Myozyme
   - Questions about the Myozyme SIP

Key messages

The knowledge and understanding of the following identified key messages that the SIP is intended to convey will be evaluated in the survey:

- IARs may occur during the infusion or during the hours following infusion. Hypersensitivity/anaphylactic reactions, some of which are IgE mediated, have been reported and generally occurred during or shortly after initiation of Myozyme infusion.
- Patients who develop IgE antibodies should be monitored more closely during administration of Myozyme since they appear to be at a higher risk for the occurrence of IARs and/or anaphylactic reactions.
- Baseline serum sample collection prior to the first infusion is strongly encouraged.
- It is recommended to perform urinalysis periodically in patients with high IgG antibody titres.

- It is recommended that patients be monitored for IgG antibody regularly.
- Treating physicians are strongly encouraged to collect samples for testing of IgE, complement activation and tryptase for patients who experience moderate to severe or recurrent IARs suggestive of hypersensitivity reactions.
- Skin testing may be performed at the discretion of the treating physician in patients who experience an IAR that is suggestive of an IgE-mediated reaction at least 48h after infusion and preferably >3 weeks after anaphylactic episode.
- Medical support measures, including cardiopulmonary resuscitation equipment should be readily available when Myozyme is administered.
- The use of antihistamines for pre-treatment is not recommended in patients with previous IgE mediated hypersensitivity reaction.
- Exposure to beta blockers may exacerbate anaphylactic reactions and is a relative contraindication when a patient is at a risk of anaphylaxis. Beta-blockers are also a relative contraindication for epinephrine/adrenaline administration
- The HCPs are encouraged to report suspected ARs via the national reporting system
- The HCPs should encourage patients to enroll in the Pompe Patient Registry

Endpoints

To address the primary objective: To assess awareness, readability, usage, usefulness, understanding, clinical knowledge and behavioral implementation of key safety information contained in the updated SIP as compared to the previous version of the SIP among HCPs:

The updated SIP will be compared to the previous version of the SIP for differences in:

- Percentage of HCPs who are aware of the existence of the SIP.
- Usage of the SIP will be measured by:
    - the percentage of HCPs for individual responses to the question on the extent to which the SIP has been incorporated into the procedures for the management of Pompe patients in their centres
    - the percentage of HCPs for individual responses to the question on the type of access the HCP has to the SIP
- Levels of HCPs' knowledge and understanding related to the key safety messages
- Behavior of HCPs around key safety messages
- Levels of readability
- Degree of usefulness
- Mean scores for questions grouped by objectives that can be assigned as having a 'correct' response: clinical knowledge, understanding, usage and usefulness.

To address the secondary objectives #1: To assess distribution of the updated SIP and format of the SIP (paper or electronic) as compared to the previous version of the SIP among HCPs.

The updated SIP will be compared to the previous version of the SIP for differences in proportion of HCPs who have received the SIP.

To address the secondary objectives #2: To assess the opinion of HCPs of the appropriateness of the updated SIP as compared to the previous version of the SIP among HCPs.

The updated SIP will be compared to the previous version of the SIP for differences in opinion of HCP.

To address the secondary objectives #3: To identify major determinants of the degree of awareness, readability, usage, usefulness, understanding, knowledge, and behavioural implementation of key safety messages contained in the updated SIP as compared to the previous version of the SIP among HCP.

The updated SIP will be compared to the previous version of the SIP for differences in determinants of response: type of HCP, country, age and gender of HCP, years in specialty, number of patients for whom Myozyme was prescribed in the previous 12 months, type of practice, type of institution (academic or non-academic) and participation in the Pompe Registry.

To address the exploratory objective: to document the reasons for lack of immunological testing with the updated and previous versions of the SIP among HCPs.

The updated SIP will be compared with the previous SIP for differences in qualitative reasons for lack of immunological testing among HCPs.

Variables

The questionnaire will assess the following concepts:

Table 2. Summary of concepts in the HCP survey

Survey concept	**Operational definition**
Awareness of the existence of the SIP	Knowledge that there is a Myozyme SIP in place
Distribution and format of the SIP	Receipt of the SIP by the HCP Format of the SIP (electronic or paper)
Readability/ understanding of the SIP	Clarity, conciseness, completeness, brevity, necessity
Usefulness of the SIP	Practical applicability of the SIP. The following 5 dimensions will be assessed: • dosing and administration • risk identification • management of risks • AE reporting • Immunology testing procedures
Usage of the SIP	Usage will be defined by: • The extent of implementation of the SIP into the local procedures • The type of access to the SIP • Frequency of use
Knowledge of key information on the SIP	Comprehension of key messages
Behavioural implementation of key messages	The translation of comprehension of key messages

Survey concept	Operational definition
	into concrete behaviours in clinical practice
Opinion of HCPs	Clarity, conciseness, completeness, brevity, necessity and usefulness

Practice data collected about the HCP to explore factors associated with understanding and implementation are presented in

Table 3. Other data collected about the HCP for study management purposes are:
- HCP identification: ID, name, gender, country, postal and email addresses
- Site name or number

Table 3. Definition of variables of interest for the HCP survey

Variable	Operational definition
Age	Age of the HCP
Gender	Gender of the HCP
Country	Country where the HCP practices
HCP type/unit	Physician or Nurse Neurology, paediatrics, endocrinology, metabolic unit, genetics, neuromuscular unit and other
HCP role	Role that the HCP has performed in the treatment with Myozyme
Years in specialty	Number of years managing patients with Pompe disease
Type of institution	Academic or non-academic
Number of patients treated with Myozyme in the unit/ department/ service in the preceding 12 months	Number of patients treated with Myozyme in the unit/service/department in the previous year
Participation in the Pompe Registry	Participation and reasons for not participation in the Pompe Registry

9.4 DATA SOURCES

A web-based electronic data capture (eDC) system will be used to collect HCP responses to the questionnaire. The questionnaire will be self-administered (closed-ended questions) and can be completed at the participants' convenience. Participants will not be able to go back and change answers to previous questions. This restriction minimises the likelihood of the respondent searching for answers via the web or other sources. Participants will also not be allowed to access the questionnaire once it has been completed and submitted.

Translation and Cognitive Pretesting
This qualitative methodology will be carried out to ensure that the HCP questionnaire is readable, understandable and easy-to-use. The approved version of the questionnaire will be cognitively pretested by HCPs and translated into local languages. Cognitive interviews with 2 physicians and 2 nurses will be carried out to conceptually review the original approved version (in English) of the questionnaire. Trained interviewers will ask participants to complete the questionnaire while 'thinking aloud' and describe their thinking and thought processes as they answer each question,

each section and the questionnaire as a whole. The results will be used to optimize instructions, guidance, wording, response choices, as well as language and cultural differences to ensure appropriateness in each participating country. Once the original version of the questionnaire has been conceptually reviewed in the UK, the new version of the questionnaire will then be translated into the local languages (and back-translated) of each of the countries allowing for flexibility in regional translation, whilst maintaining the same core meaning. The local versions will be cognitively pretested by 2 physicians and 2 nurses in each of the participating countries following the aforementioned procedure. Modifications may be made based on the findings of these cognitive tests and some changes are expected to accommodate country-specific differences. Country-specific differences will be described and appended to the final study protocol.

9.5 STUDY SIZE

9.5.1 Determination of sample size

The estimation of the sample size is based on the ability to detect differences in the primary endpoints between responses to wave 1 survey (related to the previous version of the SIP) and to wave 2 survey (related to the updated SIP). No information is available on the expected values for the primary outcomes. As the number of eligible HCPs is expected to be limited comparisons will primarily concentrate on continuous endpoints, such as knowledge, usefulness or readability. For endpoints measured on a continuous scale from 0 to 10, a sample of 100 physicians and nurses will allow for the detection of a minimum difference of 0.25 points between wave 1 and 2, with 95% precision and 80% power, using a two-way paired t-test (see Table 4).

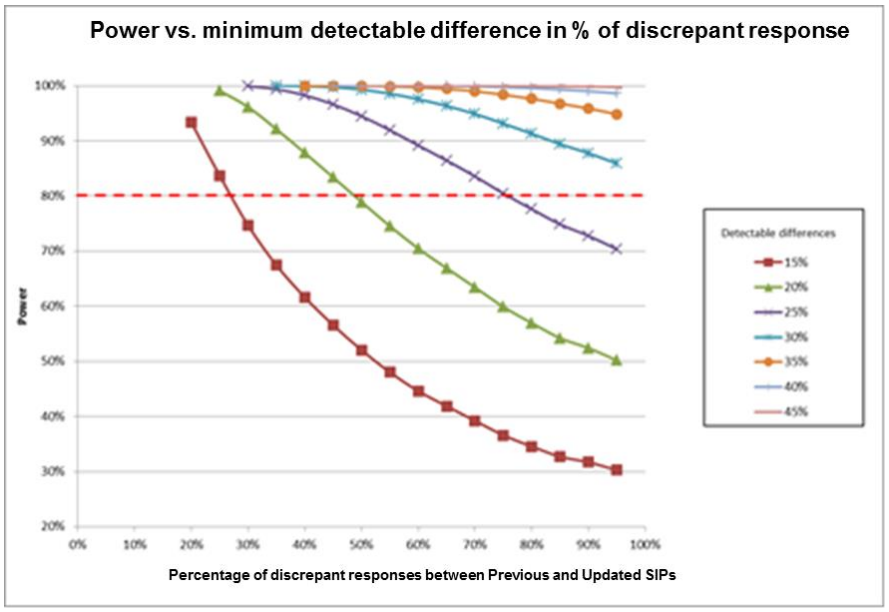
Table 4. Power for detecting absolute pre-post differences in continuous endpoints: usefulness / readibility / knowledge

Absolute differences	Sample size							
	50	100	150	200	250	300	350	400
0.25	44.7%	79.0%	95.3%	99.5%	99.9%	100.0%	100.0%	100.0%
0.50	95.5%	99.9%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
0.75	99.9%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
1.00	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
1.25	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
1.50	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
1.75	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
2.00	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
2.25	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
2.50	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
2.75	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
3.00	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

The 95% confidence intervals around estimates of usefulness, readability or knowledge scores for standard deviations of 1, 2, 3 and 4 points are 0.18, 0.36, 0.53 and 0.71, respectively.

Additionally, 100 HCPs will allow detection of absolute differences of 20%, 25% and 30% in the categorical primary endpoints between the two surveys when the percentage of discordant pairs is 25% - 50%, 30% - 75% and above 35%, respectively, using a two-sided McNemar test, with 95% confidence and greater than 80% power (see Figure 4).

Figure 4. Power vs. percentage of discordance by minimum detectable difference



As shown in Table 5, for 100 HCPs precision around the estimated percentage of knowledge and understanding of the SIP would range from 6.4 to 10.2% a 10% absolute increase in knowledge.

Table 5. Precision around an estimated percentage

Percentage of knowledge of the SIP	Sample size								
	50	75	100	150	200	250	300	350	400
50%	14.5%	11.8%	10.2%	8.3%	7.2%	6.4%	5.8%	5.4%	5.0%
40% /60%	14.2%	11.6%	10.0%	8.1%	7.0%	6.3%	5.7%	5.3%	4.9%
30% / 70%	13.4%	10.9%	9.4%	7.6%	6.6%	5.9%	5.4%	5.0%	4.6%
80%	11.9%	9.6%	8.3%	6.7%	5.8%	5.2%	4.7%	4.3%	4.1%
90%	9.3%	7.4%	6.4%	5.2%	4.4%	3.9%	3.6%	3.3%	3.1%

A high participation rate of approximately 80% from HCPs is expected due to the rarity of the disease and the high degree of specialization of the HCPs involved, although response rates may vary by country and specialty.

9.5.2 Sample size

Each survey wave will aim to recruit approximately 50 prescribers and 50 nurses in the 6 participating countries (France, Germany, Italy, Spain, the UK and Poland).

9.6 DATA MANAGEMENT

A data management plan (DMP) will be written to guide all aspects of data handling. It will include all data forms and annotations, data system dictionaries, data cleaning specifications, testing documentation and summaries, database documentation, merging of datasets, transfer of files, change control documentation and the eDC HCP questionnaire data, including any necessary country-specific modifications and interim analyses. Data entered into the eDC HCP questionnaire will be subject to edits and internal logistical checks to ensure high quality data. Data managers and other staff at OXON will perform user acceptance testing before the eDC questionnaire is released to survey participants.

The identities of HCPs taking part in the surveys will be controlled by the use of unique identification codes. These source ID numbers will be held securely on a separate system from that used to host the survey application, and this data will be used solely for the purpose of identifying whether the HCP has completed the survey.

9.6.1 Data collection schedule

As two survey waves will be conducted, data will be collected at 2 different time points: pre-implementation and post-implementation of the updated SIP. The planned length of the data collection period for each wave is three months. Based on potential country specific requirements, the start/end of the data collection period may be different between countries. Wave 1 will be initiated after approval of the protocol by the PRAC and wave 2 will be conducted after the implementation of the SIP in the participating countries, at least 18 months after the end of wave 1. Cross-sectional data will be collected through an on-line questionnaire that will be completed by the participating HCPs.

9.6.2 Data collected in the HCP Questionnaire

The questionnaire will be completed by the HCP who will provide data listed in Table 6:

Table 6. Description of data collected in the HCP questionnaire

Concept	Data collected
HCP identification	ID, name, gender, country, postal and email addresses
Site identification	Site name or number
Screening	HCP type: Nurse or physician

Concept	Data collected
	Unit type: Neurology, paediatrics, endocrinology, metabolic unit, genetics, neuromuscular unit and other
	Inclusion criterion: HCP has managed at least one patient in the preceding year on Myozyme for Pompe disease through prescribing, monitoring or administering Myozyme therapy
	Exclusion criterion: Current or ex-employee of Genzyme, a Sanofi Company or Sanofi.
	Participation in a similar survey about the Myozyme Safety Information Packet in the preceding 2 years (wave 2 specific)
Quality control variable	Whether the HCP has read the SIP before or during the survey
Primary objective: awareness of the existence of the SIP	Knowledge that there is a Myozyme SIP in place and whether it has been read by the HCP
Primary objective: assessment of usage of the SIP	Extent of implementation of the SIP into the local procedures Type of access to the SIP Frequency of use
Primary objective: assessment of usefulness of the SIP	Usefulness of the SIP about dosing and administration, risk identification, clinical management of associated risks, immunology testing procedures and AE reporting
Primary objective: assessment of readability/ understanding of the SIP	Level of readability and understanding: clarity, conciseness, completeness, brevity and necessity
Primary objective: assessment of knowledge of key information on the SIP	Knowledge of risks associated with Myozyme, pre-treatment recommendations in patients with previous IgE mediated hypersensitivity reactions, medical support measures during the administration of Myozyme, tests to be performed routinely before administration, type of patients at a higher risk for injection associated reactions, recommendations for periodic urinalysis and skin testing.
Primary objective: assessment of implementation of behaviour	Type of tests performed in patients treated with Myozyme. How often HCPs refer to the SIP How often HCPs encourage patients to register in the Pompe Registry How often HCPs report adverse events associated with Myozyme
Secondary objective #1: assessment of distribution and format	Receipt of the SIP by the HCP Format of the SIP (electronic or paper)
Secondary objective #2: assessment of opinion of HCPs	Clarity, conciseness, completeness, brevity, necessity and usefulness
Secondary objective #3: determinants of response	Age of the HCP
	Gender of the HCP
	HCP role: Role that the HCP has performed in the treatment with Myozyme
	Years in specialty: Number of years managing patients with Pompe disease
	Type of institution: academic or non-academic
	Number of patients treated with Myozyme in the unit/ department/ service in the preceding 12 months
	Participation and reasons for not participation in the Pompe Registry
Exploratory objective	Reasons for lack of immunological testing

9.6.3 Screening log (if applicable)

Not applicable

9.6.4 Patient data

Not applicable

9.6.5 Procedure for withdrawal of patients from study follow-up schedule

Not applicable

9.6.6 Logistic aspects

Not applicable

9.7 DATA ANALYSIS

This section presents the key analyses planned for the survey.

The survey will include two analysis phases:

- Interim analysis which is planned to be performed once the data collection for wave 1 of the survey is completed and will report the results of this first wave.

- Final analysis which will be carried out at the end of the data collection period for wave 2 of the survey. The final analysis will not only include the analysis of data from the second wave, but also the longitudinal analysis of changes observed from wave 1 to wave 2 of the survey. The final statistical report will include all results from the interim and the final analyses.

A detailed SAP will be developed and approved before final database lock of survey wave 1 and will include methods of analysis and presentation and table shells. All analyses will be performed using SAS 9.3 (or higher) statistical software (SAS, Cary, North Carolina, USA).

Assessment of representativeness

Survey representativeness is important to assess the extent to which the results of the evaluation can be generalized to clinical practice in each country. Response rates for recruitment and screening will be detailed in the study report.

Survey drop-out rates will also be presented for each survey. Data will be analyzed as presented from the survey results.

The rate of HCPs who responded to both surveys will also be detailed in the study report. A flow-chart will describe the distribution of HCPs.

Contacted HCPs will be divided into 6 different datasets:

- Physicians who agree to participate in the survey
- Physicians who refuse to participate in the survey
- Physicians who do not respond to invitations to participate in the survey
- Nurses who agree to participate in the survey
- Nurses who refuse to participate in the survey
- Nurses who do not respond to invitations to participate in the survey

Representativeness will be assessed by performing descriptive analyses on the data collected for each HCP dataset (country, type of centre, volume of patients) and making comparisons, separately for nurses and physicians, between HCPs who agree vs. HCPs who refuse vs. HCPs who do not respond vs. national statistics (where available). Analyses will be conducted at country level and globally.

Missing data

Responses to questions in the surveys may be missing or illegible. They will be dealt with in the following ways:

- For questions relevant to the primary endpoints, missing and illegible data for a question will be assumed to be either 'incorrect' for questions that have responses that can be assigned as correct and incorrect, or alternatively to the uncertain category where a correct/incorrect cannot be assigned.
- For all other variables, missing and illegible data will be ignored.

Missing data may affect the patients who can be included in certain multivariate analyses, and this will be detailed in the SAP.

General statistical considerations

Descriptive statistics will be presented for all variables of interest.

Unless otherwise specified, two-sided tests of statistical hypotheses will be conducted with a 5% significance level. Corresponding 95% confidence intervals will be reported as appropriate. No adjustment will be made for multiple comparisons or for multiple analyses.

Categorical data will be summarized by counts and percentages. Continuous data will be summarized using number, mean, standard deviation (SD), median, quartiles, minimum and maximum and in the case of non-normally distributed data, median, range and interquartile range. Illustrative graphs with the distribution of variables will be provided on a set of selected key variables for both surveys.

Pre- and post- measures of HCPs' knowledge, usage, understanding and implementation of behavior will be compared with the appropriate tests for related samples in the Paired Analysis Population (paired t-test for normally distributed continuous variables, Wilcoxon signed rank test for non-normally distributed continuous variables, McNemar, chi-square for categorical variables, and Kruskal-Wallis, Kendall's tau, Goodman-Kruskal gamma for ordinal variables). For survey wave 2, tests for Paired Analysis Population and Independent Analysis Population as independent

samples will be used for comparison (t-test for normally-distributed continuous variables, Mann-Whitney U for non-normally distributed continuous variables, Kruskal-Wallis for ordinal, and chi-square test for categorical variables). Non-parametric techniques will be used to test for differences for the comparison of variables for small samples due to the condition of orphan drug for a rare disease (U Mann-Whitney, Wilcoxon signed rank sum, or Friedman tests). All analyses will be performed using two-sided alpha values of 0.05.

The study of associations between the endpoints and independent variables will start with univariate analysis, with the appropriate statistical techniques depending on the type of endpoint and its distribution, as described above. After univariate associations have been identified, multivariate analysis, if necessary and appropriate, will try to obtain determinants of the primary endpoint. The multivariate analysis techniques to be used will also depend on the type and distribution of the endpoint. Generalized Linear Models (GLM) will be used, with multivariate linear regression for continuous normally-distributed dependent variables, logistic regression for dichotomous outcomes, and others as necessary (polythomous ordinal logistic regression, poisson regression, etc…). Modelling will follow a stepwise scheme were independent variables that result associated in the univariate analysis will be entered into the model by blocks of variables. Variables will be kept into the model if they show an association with the dependent variables at the time when their block is entered into the model, even though after entering further consecutive blocks of variables the strength of the association disappears ($p>0.05$). The order of the sequence of blocks corresponds to the following scheme:

1. HCPs sociodemographic characteristics
2. HCP characteristics
3. Institution characteristics
4. HCP experience in the management of Pompe disease patients and use of Myozyme

Descriptive analysis

The study populations for each survey will be described. Summary statistics will include:

- The sociodemographic characteristics of the HCP (age group and gender),
- The HCP professional profile (type of HCP, years of experience),
- Experience with Pompe disease (number of patients in the last 12 months, role in the prescription of Myozyme)
- Characteristics of their Department, Service or Unit (academic or not, specialized nurses, workload, number of Pompe disease patients per year)

Additionally, for survey wave 2, summary statistics will be provided by the subgroups defined by the Paired Analysis Population and Independent Analysis Population. If a sufficient number of HCPs is available in each subgroup, comparisons will assess differences between these two analysis sets.

All questionnaire variables that address the study objectives will be summarized for each survey according to the sections of the questionnaire to which they belong.

9.7.1 Primary analysis

To address the primary objective: To assess awareness, readability, usage, usefulness, understanding, clinical knowledge and behavioral implementation of key safety information contained in the updated SIP as compared to the previous version of the SIP among HCPs:

The primary analysis, for each survey wave, will calculate:

- The total number of HCPs answering all relevant questions for an endpoint
- For the assessment of awareness:
    - Percentage of HCPs responding that they know that there is a SIP for Myozyme
    - Percentage of HCPs responding that they have read the SIP
- For the assessment of usage:
    - Percentage of HCPs responding that they have used the SIP
    - The mean score for the frequency of usage
    - The mean score for the access to the SIP
    - An overall score of usage of the SIP defined as frequency * accessibility
- For the assessment of usefulness:
    - The mean score of the responses to the numerical rating scale items addressing usefulness of the SIP as a guideline document for dosing and administration, management of risks, AE reporting, risk identification and testing procedures related to Myozyme
    - The overall mean score of usefulness of the SIP for all the above items
- For the assessment of understanding / readability
    - The mean score of the responses to the numerical rating scale items addressing clarity, conciseness, completeness and brevity
    - The overall mean score of understanding of the SIP for all the above items
- For the assessment of knowledge of key messages in the SIP
    - The percentage of HCPs providing correct answers to knowledge and comprehension questions of key messages of the SIP
    - The overall percentage of correct answers to knowledge and comprehension questions of key messages of the SIP
- For the assessment of behavioral implementation of key messages in the SIP:
    - Percentage of HCPs who offer the inclusion in the Pompe registry to all their patients
    - Percentage of HCPs who perform the immunological tests appropriately

To assess the effectiveness of the updated SIP in the primary endpoints described above, comparisons of these endpoints between the two surveys will be made. These comparisons will be

done separately for those patients who responded to both surveys with statistical techniques for related samples, and, if the number of HCPs allows for it, for those who only answered one of the surveys with statistical techniques for independent samples. Continuous variables, such as the scores for usage, usefulness, readability and knowledge will be compared with t-tests for paired or independent samples when appropriate if the variables are distributed normally. Otherwise, non-parametric Wilcoxon's signed rank sum for related samples, or Mann-Whitney's U tests for independent samples will be the statistical technique. Categorical data such as the percentages of HCPs aware of the SIP or whose behavior is consistent with safety key messages will be compared with McNemar or chi-square tests for related samples, chi-square for independent samples. Ordinal variables such us the frequency of usage or the access to the SIP will be compared with Kruskal-Wallis, Kendall's tau, Goodman-Kruskal gamma

If numbers allow for comparison of answers to the questionnaires for the updated SIP between the Paired Analysis Population and the Independent Analysis Population of survey wave 2, these analyses will be done to study the impact of the Hawthorne effect in responses to the questionnaire.

The results will be presented in total and stratified by the following factors:

- Country
- HCP type,
- Practice setting,
- RM tool users vs. non-users

HCP types will be categorized for analysis within individual countries and across the participating countries as a whole, by grouping the response options to survey questions on HCP type.

9.7.2 Secondary analysis

To address the secondary objectives #1: To assess distribution and format (electronic or paper) of the updated SIP as compared to the previous version of the SIP among HCPs.

To assess the effective distribution of the SIP:

For each survey it will be calculated:

- The percentage of HCPs who respond that they know the existence of the SIP and have received and have read the SIP
- The percentage of HCPs who have received the SIP by source of information
- The percentage of HCPs who have not received or read the SIP
- The percentage of HCPs who received the SIP after their first prescription or administration of Myozyme
- The percentage of HCPs who received the SIP in the last 18 months

To compare the effective distribution of the updated SIP, all the above percentages will be analysed with the appropriate statistical techniques to compare categorical data for related samples and independent samples (Paired Analysis Population vs. Independent Analysis Population of survey wave 2).

If numbers allow for comparison of answers to the questionnaires for the updated SIP between Paired Analysis Population and Independent Analysis Population of survey wave 2, these analyses will be done to study the impact of the Hawthorne effect in responses to the questionnaire.

The results will be presented in total and stratified by the following factors:

- Country
- HCP type,
- Practice setting,
- RM tool users vs. non-users

HCP types will be categorized for analysis within individual countries and across the participating countries as a whole, by grouping the response options to survey questions on HCP type.

To address the secondary objectives #2: To assess the opinion of HCPs of the appropriateness updated SIP as compared to the previous version of the SIP among HCPs

To assess the opinion of HCPs on the SIP it will be calculated:

- The percentage of HCPs who scored <3 points, or >6 points to all questions regarding clarity, conciseness, completeness, brevity, necessity and usefulness in each of the questionnaires.

To compare the effective opinion of HCPs about the updated SIP, the percentages will be analysed with the appropriate statistical techniques to compare categorical data for related samples (Paired Analysis Population) and independent samples (Paired Analysis Population vs. Independent Analysis Population of survey wave 2).

If numbers allow for comparison of answers to the questionnaires for the updated SIP between the Paired Analysis Population and the Independent Analysis Population of survey wave 2, these analyses will be done to study the impact of the Hawthorne effect in responses to the questionnaire.

The results will be presented in total and stratified by the following factors:

- Country
- HCP type,
- Practice setting,
- RM tool users vs. non-users

HCP types will be categorized for analysis within individual countries and across the participating countries as a whole, by grouping the response options to survey questions on HCP type.

To address the secondary objectives #3: To identify major determinants of the degree of awareness, readability, usage, usefulness, understanding, knowledge, and behavioural implementation of key safety safety messages contained in the updated SIP as compared to the previous version of the SIP among HCP.

All primary endpoints will be analysed by subgroups for the study of associations at each survey. Subgroups will be determined by the following variables:

- type of HCP (physician or nurse),
- role of the HCP in the management of Myozyme,
- country,
- age group
- gender of the HCP,
- years in the specialty,
- number of patients for whom Myozyme was prescribed in the previous 12 months,
- type of practice,
- type of institution (academic or non-academic)

Univariate analysis will identify for each primary endpoint and subgroup analysis, those variables which are associated ($p<0.05$) with changes in the endpoint values. Univariate tests will be used as appropriate for the type of endpoint (continuous, categorical and ordinal) and its distribution (normality).

All those variables that are found to be associated in the univariate analysis to a primary endpoint will be later studied in multivariate analysis for that particular endpoint and survey. Multivariate analysis will depend on the type of endpoint and distribution. GLM regression models will be adjusted for covariates.

Additionally, for HCPs in the Paired Analysis Population and for the updated SIP models, covariates may include the initial values of the primary endpoint modeled. Alternatively, instead of using the primary endpoint of the updated SIP as the dependent variable, the incremental differences in the primary endpoints from baseline may be modeled (endpoint survey wave 2 – endpoint survey wave 1).

To address the exploratory objective, to document the reasons for lack of immunological testing with the updated and previous versions of the SIP among HCPs:

Descriptive summary of percentages of HCPs responding to each of the reasons for lack of immunological testing for each test.

9.7.3 Interim analysis

The interim analysis will include:

- the assessment of the representativeness of the study populations for survey wave 1,
- a complete description of the HCP population and all study variables collected in survey wave 1,

- the assessment of the primary endpoints (awareness, usage, usefulness, understanding, clinical knowledge and behavioral implementation of key safety information) contained in the SIP before its updating.
- the identification of the major determinants of these endpoints.

The methodology to be followed for these analyses will be the same as for the analyses above described.

9.8 QUALITY CONTROL

Standard operating procedures will be applied to ensure quality to all aspects of the survey conduct, data management and statistical analysis.

9.8.1 Data collection, validation and data quality control at MAH/MAH representative level

The survey may be evaluated by Genzyme internal auditors and government inspectors who must be allowed access to the questionnaires, any other study files, and study facilities. Genzyme audit reports will be kept confidential.

In addition, data generated by this survey must be available for inspection upon request by representatives of national and/or local health authorities, sponsor monitors, representatives, and collaborators, as appropriate. The investigator must notify Genzyme promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to Genzyme.

9.8.2 Data quality control at site level

Not applicable

9.9 LIMITATIONS OF THE RESEARCH METHODS

The following key considerations should be addressed: representativeness and precision due to the rarity of the condition being treated and the potential for bias in the responses.

- Representativeness, statistical power and the level of professional experience of HCPs with the disease may be affected by the low prevalence of the disease, with dispersed patients and their HCPs across geographical regions. In addition, HCPs usually are responsible for a few numbers of cases or, alternatively, belong to centres which are reference centres for that disease. To address those limitations, the sampling scheme would rank by country and number of cases per practitioner and select a convenience sample. The estimation of the sample size has considered this limitation and calculations allow for enough statistical power to detect these differences.

- HCPs who refuse to participate may limit the representativeness of the HCP survey. This will be examined by comparing participating and non-participating physicians on some key variables and with national statistics on nephrologists.

- Recall bias would equally affect the evaluation of both pre and post new SIP assessment providing the surveys are sufficiently far apart; 18 months is likely to be sufficient. Furthermore, the more experienced HCPs are likely to use testing less, so this will be a countervailing bias to that of recall bias.

- Non-response bias is a concern with any voluntary survey. This is a challenge, among HCPs in view of the demands on their time and the low honoraria that is paid for questionnaire completion. This survey will minimise non-response bias by offering a reasonable incentive that compensates respondents for personal time spent but one that is not considered coercive.

- Measures to minimise HCP response bias with online questionnaires are: all questions are programmed to ensure that they are presented in an appropriate sequence, questions must be answered in sequence, skipping ahead to later questions is not permitted, questions cannot be changed once completed and skip patterns to questions are clearly indicated.

- At both assessments time points, the Hawthorne effect may be present but will be minimised in those HCPs who participate in both surveys. Design of the questionnaire to avoid leading questions may help to avoid any induction bias.

- Since this is an online survey, we cannot detect whether or not HCPs attempt to utilize any reference materials while taking the survey. However, they will not be provided with any reference materials and they will not be able to change responses to questions that have been completed. HCP responses may be biased by referral to the SIP as they complete the questionnaire. This will be minimized by explaining that responses should be based on assessing what they currently know and that they should not refer to the SIP.

9.10 OTHER ASPECTS

None

10 PROTECTION OF HUMAN SUBJECTS

10.1 RESPONSIBILITIES OF THE PHYSICIAN/HEALTH CARE PROVIDERS

The HCP will perform the survey in accordance with this protocol, applicable local regulations and international guidelines. It is the HCP´s responsibility to fill in the questionnaire.

Responsibilities of MAH/MAH REPRESENTATIVE

The MAH/MAH REPRESENTATIVE is responsible for taking all reasonable steps and providing adequate resources to ensure the proper conduct of the survey.

The MAH/MAH REPRESENTATIVE is responsible for:

- Local submission(s) complying with data protection rules,
- Any other local submission(s).

10.2 ETHICAL, REGULATORY AND ADMINISTRATIVE RULES

10.2.1 Ethical principles

This survey will be conducted in accordance with the principles laid by the 18th World Medical Assembly (Helsinki, 1964) and all subsequent amendments.

10.2.2 Laws and regulations

This survey will be conducted in accordance with:

- the guidelines for Good Epidemiology Practice in Europe (9).
- the European Network of Centres of Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology (10).
- Good Pharmacovigilance Practices (GVP) module VIII: ‘Post-authorization safety studies’ (8).
- GVP Module XVI: ‘Risk minimization measures - Selection of tools and effectiveness indicators’ (11).
- Practical Approaches to Risk Minimisation for Medicinal Products (12)

According to regulatory requirements in each of the participating countries, local approvals from ethics committees are not required in this study as only data from HCPs, not from patients, will be collected.

10.2.3 Data protection

The HCP's personal data which may be included in the MAH/MAH REPRESENTATIVE database shall be treated in compliance with all local applicable laws and regulations.

When archiving or processing personal data pertaining to the HCP, the MAH/MAH REPRESENTATIVE shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

10.2.4 Insurance

Not applicable

10.2.5 Secrecy agreement

All material, information (oral or written) and unpublished documentation provided to the HCP (or any action carried out by the MAH/MAH representative on their behalf), including the present protocol and the questionnaire, are exclusive property of the MAH/MAH representative.

These materials or information (both global and partial) cannot be given or disclosed by the HCPs or by any person of her/his group to unauthorized persons without the prior formal written consent of the MAH/MAH representative.

The HCP shall consider as confidential all the information received, acquired or deduced during the study and will take all necessary steps to ensure that there is no break of confidentiality, other than for information to be disclosed by law.

10.2.6 Record retention

The HCP shall arrange for the retention of study documentation until the end of the study.

It is recommended that the HCP retains the study documents at least five years (5) after the completion or discontinuation of the study, unless otherwise specified in the HCP Agreement in line with additional standards and/or local laws.

However, applicable regulatory requirements should be taken into account in the event that a longer period is required.

10.2.7 Discontinuation of the study

The MAH/MAH representative can decide at any time and for any reason to discontinue the study; the decision will be communicated in writing to the participating HCP.

Similarly, should the HCP decide to withdraw from the study, she/he will have to inform the MAH/MAH representative in writing.

10.2.8 MAH/MAH representative audits and inspections by competent authorities

The HCP agrees to allow the MAH/MAH representative auditors/Competent Authorities inspectors to have direct access to his/her study records for review, being understood that this personnel is bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The HCP will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

Any result and information arising from the inspections by the competent authorities will be communicated by the HCP to the MAH/MAH representative.

The HCP shall take appropriate measures required by the MAH/MAH representative to take corrective actions for all problems found during the audit or inspections.

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS/PV DATA

This study is not designed to collect information on individual adverse events (AEs)/PV Data associated with the use of Myozyme. However, it is possible that, during the conduct of the surveys, respondents may spontaneously provide information that meets the criteria for an AE/PV Data.

If during the course of the study OXON becomes aware of any Pharmacovigilance (PV) data regarding any Sanofi/Genzyme product, it shall be reported to the competent Genzyme PV department within one business day from the date of OXON becoming aware of such data by:

- completing the PV Reporting Form
- and sending it to the local Genzyme PV department (Table 7) by email to the following email address:

Table 7. Contact information of local Genzyme PV affiliates in the participating countries

Country	Name	Local affiliate PV mailbox	Phone number	Fax number
France	Magda Bensetti	france.pharmacovigilance@genzyme.com	Office:+33 1 30 87 34 70 Mobile:+33 825 801 051	+33 1 30 87 26 69
Germany	Juergen-Hans Schmidt,	Arzneimittelsicherheit@sanofi.com	Office:+49 69 305 4391	+ 49 69 305 177 66
Italy	Andrea Chiarenza	Farmacovigilanza.italia@sanofi.com	+39 02 3939 4716	+39 02 3939 4716
Poland	Anna Korytkowska	ADR.PL@sanofi.com	Office:48 22 2800 830	+ 48 22 28 00 603
Spain	Javier Marfa	es-farmacovigilancia@sanofi.com	Office:+34 934859505	+ 34 93 489 5505
UK	John Solomon	Uk-drugsafety@sanofi.com	Office:+44 1483 55 4467	+44 1483 55 4806

The identified possible sources of PV Data are:

- The interviewer, in the cognitive interviews that will be performed during the pre-testing of the survey questionnaire prior to its implementation, may detect an adverse event or any reportable PV data. The interviewer will be trained by Genzyme in AE/PV Data identification and reporting prior to the conduct of the cognitive interviews. If an AE/PV Data is reported s/he will complete the 'PV Reporting form' together with the HCP who reported the AE/PV Data, and submit it to the country Genzyme PV unit immediately

(email: see Table 7 for country Genzyme PV contact details). The information in the form will be translated into English (when required) and submitted to Genzyme PV country local affiliate within 1 business day by e-mail.

- Online respondents to the electronic survey who may report any AE/PV Data by completing the 'PV Reporting form' and forwarding it immediately to (email:mailto: see Table 7 for country Genzyme PV contact details). If the report is completed in the local language, the information in the form will be translated into English and submitted to Genzyme PV country local affiliate within 1 business day by e-mail.
- In addition, any HCP participating in the study will be provided with the telephone number and e-mail of the country PV Genzyme unit to report any AEs/PV Data.

If only limited information is initially available, follow-up reports may be required. HCPs will send, preferably by fax or e-mail, to Genzyme PV (see Table 7 for country Genzyme PV contact details) () the photocopy of all examinations carried out and the dates on which these examinations were performed. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers are properly mentioned on any copy of source document provided to Genzyme PV. For laboratory results, include the laboratory normal ranges.

11.1 SAFETY INSTRUCTIONS

All events will be managed and reported in compliance with all applicable regulations.

11.1.1 Definitions of Adverse Event (AE) and Serious Adverse Event (SAE)

An **Adverse Event** is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

A **Serious Adverse Event** is any untoward medical occurrence that at any dose:

- Results in death or;
- Is life-threatening or;
  Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization or;
- Results in persistent or significant disability/incapacity or;
- Is a congenital anomaly/birth defect;
- Is a medically important event;
- Suspected transmission of infectious agent ; is any suspected transmission of an infectious agent via a medicinal product (e.g., product contamination);

- Overdose and pregnancy could be considered as medically important event. Reporting rules are the same as for serious adverse events.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

11.1.2 PV Data

Pharmacovigilance Data" or "**PV data**" shall mean:

- Adverse Events, Serious or not;
- any Incident
- any report of misuse (with or without Adverse Events);
- any medication error; any off-label use (with or without Adverse Events);
- any overdose;
- any drug abuse;
- any lack of efficacy;
- any suspected transmission of infectious agents
- any drug exposure during pregnancy or child exposure during breastfeeding (with or without Adverse Events); and
- occupational exposure (with or without Adverse Events).

11.2 SAFETY OBSERVATIONS

The Physician should take all appropriate measures to ensure the safety of the patients as per normal practice.

11.3 OBLIGATIONS OF SANOFI/GENZYME

During the course of the study, the MAH will report safety data to health authorities according to Directive 2001/83/EC and in accordance with all applicable local and global regulations (e.g.: All serious ADR within 15 days from the date of receipt of the reports to the health Authorities; All non-serious ADR within 90 days from the date of receipt of the reports to the health Authorities for some European countries)

The MAH will report all safety observations made during the conduct of the study in the final study report.

12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

12.1 OWNERSHIP AND USE OF DATA AND STUDY RESULTS

No use of the data will be possible without the authorization of the MAH/MAH REPRESENTATIVE conducting the study

The Scientific Committee will have full access to the final data allowing for appropriate academic analysis and reporting of the study results.

12.2 PUBLICATIONS

The protocol, study status updates and report(s) will be included in regulatory communications according to the risk minimisation plan, periodic benefit-risk evaluation reports and other regulatory milestones and requirements.

The final decision to publish any manuscript/ abstract/ presentation will be made by the Scientific Committee after prior notice to the MAH/MAH REPRESENTATIVE allowing for its internal review and comments. All manuscript/ abstract/ presentation must be submitted to the internal review of the MAH/MAH REPRESENTATIVE at least forty-five (45) calendar days in advance of submission. The MAH/MAH REPRESENTATIVE may request that the MAH/MAH REPRESENTATIVE's name and/or names of one or several of its employees appear or do not appear in such publication.

The MAH/MAH REPRESENTATIVE can delay publication or communication for a limited time in order to protect the confidentiality or proprietary nature of any information contained therein.

A Publication Committee responsible for the overall publication plan can be set up upon needs. Its main mission could be:

- To define the overall publication plan including the primary publications reporting new scientific findings/data from the study
- To review and approve (or abstain) all other publications proposals and draft manuscripts regarding subsequent publications including local publications.

As this survey study is part of an evaluation programme intended to assess the effectiveness of the SIP, results should be interpreted in combination with the evaluation of safety and clinical outcomes. In view of the results obtained, the decision whether the SIP might be maintained, further updated/modified or even abandoned will be made.

13 REFERENCES

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ANNEXES

Annex 1 List of stand-alone documents

Number	Document reference number	Date	Title
2	Version 8.3	29 May 2015	Questionnaire

Annex 2 ENCePP checklist for study protocols

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). Note, the Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
Myozyme (alglucosidase alfa) Safety Information Packet effectiveness evaluation: a health care professional survey

Study reference number:
ENCEPP/SDPP/10301

Section 1: Milestones	Yes	No	N/A	Page Number(s)
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	17
1.1.2 End of data collection[2]	☒	☐	☐	17
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☒	☐	☐	17
1.1.5 Registration in the EU PAS register	☒	☐	☐	17
1.1.6 Final report of study results.	☒	☐	☐	17

Comments:
Study progress reports are not expected to be developed during the study conduct.

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

ENCePP Checklist for Study Protocols (Revision 2)

Section 2: Research question	Yes	No	N/A	Page Number(s)
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 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)	☒	☐	☐	11,18-23
2.1.2 The objective(s) of the study?	☒	☐	☐	11,12 24,25
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	12,27,28
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☒	☐	☐	11,12 24,25
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	Yes	No	N/A	Page Number(s)
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	12,26
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	12,13 30,31
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)	☒	☐	☐	39-44

Comments:

Section 4: Source and study populations	Yes	No	N/A	Page Number(s)
4.1 Is the source population described?	☒	☐	☐	12,27-29
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	12,27-29
4.2.2 Age and sex?	☐	☐	☒	
4.2.3 Country of origin?	☒	☐	☐	12,27-29
4.2.4 Disease/indication?	☒	☐	☐	12,27-29
4.2.5 Co-morbidity?	☐	☐	☒	
4.2.6 Seasonality?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	12,27-29

Comments:
Definition of some study population characteristics is not required for the study.

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	☒	☐	☐	12,13 30-32

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Section 5: Exposure definition and measurement	Yes	No	N/A	Page Number(s)
categorising exposure)				
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)	☒	☐	☐	32,33
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 and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

No drug effect is assessed

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?	☒	☐	☐	12,13 30-32
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)	☒	☐	☐	32,33

Comments:

The questionnaire was cognitively pretested before implementation in the participating countries

Section 7: Confounders and effect modifiers	Yes	No	N/A	Page Number(s)
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☐	☐	☒	
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	

Comments:

No drug effect is assessed

Section 8: Data sources	Yes	No	N/A	Page Number(s)
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	13,14 32,33
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	13,14
8.1.3 Covariates?	☒	☐	☐	32,33 13,14 32,33
8.2 Does the protocol describe the information available				

Section 8: Data sources	Yes	No	N/A	Page Number(s)
from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	13,14
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	32,33
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	13,14 32,33 13,14 32,33
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☒	☐	
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☐	☒	☐	
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☒	☐	
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Only one data source used for the study (healthcare professional questionnaire).

Section 9: Study size and power	Yes	No	N/A	Page Number(s)
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	14,33,34

Comments:

Section 10: Analysis plan	Yes	No	N/A	Page Number(s)
10.1 Does the plan include measurement of excess risks?	☐	☐	☒	
10.2 Is the choice of statistical techniques described?	☒	☐	☐	14,15 37-44
10.3 Are descriptive analyses included?	☒	☐	☐	14,15 37-44
10.4 Are stratified analyses included?	☒	☐	☐	14,15 37-44
10.5 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☒	

Comments:

No drug effect is assessed

Section 11: Data management and quality control	Yes	No	N/A	Page Number(s)

Section 11: Data management and quality control	Yes	No	N/A	Page Number(s)
11.1 Is information provided on the management of missing data?	☒	☐	☐	38
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	35
11.3 Are methods of quality assurance described?	☒	☐	☐	44
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	44
11.5 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:
Protocol and results will be sent and reviewed by EMA/PRAC

Section 12: Limitations	Yes	No	N/A	Page Number(s)
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	44,45
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	44,45
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	44,45
12.3 Does the protocol address other limitations?	☒	☐	☐	44,45

Comments:

Section 13: Ethical issues	Yes	No	N/A	Page Number(s)
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	46-48
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	46-48
13.3 Have data protection requirements been described?	☒	☐	☐	46-48

Comments:

Section 14: Amendments and deviations	Yes	No	N/A	Page Number(s)
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	16

Comments:

Section 15: Plans for communication of study results	Yes	No	N/A	Page Number(s)
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	52

Section 15: Plans for communication of study results	Yes	No	N/A	Page Number(s)
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	52

Comments:

Name of the main author of the protocol: NAWAB QIZILBASH .

Date: 24 /09/2015

Signature: 

Annex 3 Additional information

None