EPIDEMIOLOGY STUDY PROTOCOL

Fabrazyme (agalsidase beta) home infusion educational materials effectiveness evaluation: a survey for healthcare providers and patients/caregivers

agalsidase beta

Study type:	Post Approval Safety Study
Company:	Sanofi
Version Number/Status:	4.0/Final Revised Protocol
Study number:	AGALSC08994

This study will be conducted in accordance with
Sanofi standard operating procedures for GPE epidemiologic studies

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Date: 22-Sep-2018 Total number of pages 33

PASS information:

Title:	Fabrazyme (agalsidase beta) home infusion educational materials effectiveness evaluation: a survey of healthcare providers and patients/caregivers
Protocol version identifier	4.0/Final
Date of last version of protocol	22-Sep-2018
EU PAS register number (if applicable)	EUPAS23142
Active substance	Agalsidase beta
Medicinal product	Fabrazyme®
Product reference	EU/1/01/188/001-006
Procedure number	EMEA/H/C/000370, MEA 60.4
Marketing authorization holder(s)	Genzyme Europe B.V.
Joint PASS	No
Research questions and objective(s):	The objective of this study is to assess the effectiveness of the agalsidase beta (Fabrazyme®) home infusion educational materials from both the healthcare provider (HCP) and the patient perspectives. Effectiveness will be measured through questions on knowledge and understanding of key content areas. Implementation of the logbook around the key content areas will also be used to assess effectiveness of the materials
Country(-ies) of study	Finland, France, Italy, Norway and United Kingdom
Author	[redacted]

MARKETING AUTHORIZATION HOLDER(S)

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

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1 LIST OF ABBREVIATIONS

ADR:	Adverse drug reaction
EFPIA:	European Federation of Pharmaceutical Industries and Associations
EMA:	European Mediciens Agency
EU:	European Union
HCP:	Healthcare provider
MAH:	Marketing authorization holder
PRAC:	Pharmacovigilance risk assessment committee
PV:	Pharmacovigilance
RMP:	Risk management plan
UK:	United Kingdom

2 RESPONSIBLE PARTIES

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

- Marketing Authorization Holder (MAH)
- MAH representative

2.1 MARKETING AUTHORIZATION HOLDER

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

2.2 MAH REPRESENTATIVE

The MAH representative for this survey is Adelphi Research, a contract research organization delegated to serve as survey coordinating center for this survey. The MAH representative is responsible for the operational conduct of the survey including recruiting of the participating HCPs and patients/caregivers 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 analysis and produce the planned interim and final study reports.

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3 SYNOPSIS

Title

Fabrazyme (agalsidase beta) home infusion educational materials effectiveness evaluation: a survey of healthcare providers and patients/caregivers

Rationale and background

Fabrazyme (agalsidase beta) is a drug used to treat Fabry Disease. As part of the Fabrazyme risk management plan (RMP), education materials for home infusion therapy have been developed to serve as resources for both treating HCPs and patients.

The Pharmacovigilance Risk Assessment Committee (PRAC), requested a study to measure the effectiveness of the Fabrazyme education materials on home infusion. To comply with this request, two surveys are proposed to be conducted among 1) HCPs and 2) patients and/or patient caregiver.

Research question and objectives

The overall objective of this study is to assess the effectiveness of the home infusion educational materials from both the healthcare provider and the patient /caregiver perspectives. Effectiveness will be measured through questions on knowledge and understanding of key content areas. Implementation of the logbook around the key content areas will also be used to assess effectiveness of the materials

The primary objectives are to determine:

- The level of knowledge and understanding regarding key content areas of the educational materials including:
  - Evaluation of home infusion (HCP)
  - Elements to address when training the patient/caregiver
  - Actions to be taken in case of an adverse event
- Implementation of the logbook (owned by the patient but reviewed by the HCP)

Study design

Cross-sectional survey to be completed independently by HCPs and patients/caregivers

Population

The study will be conducted among two populations

1. HCPs who prescribe, monitor, oversee the management, and/or provide in person medical supervision of patients on Fabrazyme home infusion (Treating physicians and/or infusion nurses) across 5 European Union (EU) markets (France, United Kingdom (UK), Italy, Finland, Norway)
2. Patients (and or caregivers looking after patients) who receive Fabrazyme by home infusion across 5 EU markets (France, UK, Italy, Finland and Norway)

Variables
The HCP and patient surveys will be comprised of

A) Screening section for eligibility and demographics

B) Main questionnaire for eligible subjects collecting data relating to

HCP survey:

- Key performance indicators; awareness and usefulness of materials
- Use of educational materials for evaluating and selecting patients for home infusion and training
- Handling Adverse Reactions (ARs)
- Implementation of the logbook.

Patient/caregiver survey:

- Material use and distribution and nurse involvement
- Usefulness and understanding of educational materials
- Knowledge and behavior when preparing and administering Fabrazyme
- Implementation of the logbook
- Handling ARs

Data sources
Data sources will include:

- HCP materials: Screener, Self-administered online survey questionnaire
- Patient materials: Screener, Self-administered online survey questionnaire

Study size
A total sample size of 34 HCPs and 18 Fabry patients (or their caregivers) is targeted.

Data analysis
The analysis will be cross-sectional and descriptive. Categorical data will be summarized by counts and percentages. Continuous data will be summarized using number, median, minimum and maximum values. Missing data will be noted for each variable.

4 AMENDMENTS AND UPDATES

None

5 MILESTONES

Milestone	Planned date
1st Protocol submission	28 February 2018
Revised protocol submission	27 July 2018
Start of study	November 2018
End of data collection	April 2019
Final report of study results	August 2019
Potential publication of results	Post final report

6 RATIONALE AND BACKGROUND

6.1 BACKGROUND

Fabrazyme (agalsidase beta) indication and administration

Fabrazyme contains recombinant human α-galactosidase A (r-hαGAL) as the active ingredient. Fabrazyme is indicated for long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry disease. Fabrazyme should be supervised by a physician experienced in the management of patients with Fabry Disease or other inherited metabolic diseases. The recommended dose of Fabrazyme is 1 mg/kg body weight administered once every 2 weeks as an intravenous infusion.

Infusion of Fabrazyme at home may be considered for patients who are tolerating their infusions well. The decision to have a patient move to home infusion should be made after evaluation and recommendation by the treating physician.

Additional Risk Minimization

As part of the Fabrazyme risk management plan (RMP, version 1.2, 19 September 2011), additional risk minimization activities are included to educate patients and HCPs on key elements of Fabrazyme infusion in the home setting.

Educational materials have been developed and approved by European Medicines Agency (EMA) as additional risk minimization activities for Fabrazyme home infusion therapy, and serve as educational resources for both treating HCP and patients.
The Fabrazyme educational pack contains the following:

A) Home infusion manual for HCPs

B) Home infusion manual for patients

C) Summary of Product Characteristics or Package Leaflet

6.2 RATIONALE

Sanofi Genzyme has committed to the Pharmacovigilance Risk Assessment Committee (PRAC) to perform a survey among a) healthcare providers who prescribe, monitor, oversee the management, and/or provide in person medical supervision of patients on Fabrazyme home infusion and b) patients (and/ or their caregivers) who receive Fabrazyme in the home infusion setting. The survey will evaluate the effectiveness of Fabrazyme home infusion educational materials through questions on knowledge and understanding of key content areas, in addition to the implementation of the logbook.

7 RESEARCH QUESTION AND OBJECTIVES

The overall objective of this survey study is to assess the effectiveness of the education materials for home infusion therapy from both the HCP and the patient /caregivers perspectives. Effectiveness will be measured through questions on knowledge and understanding of key content areas. Implementation of the logbook around the key content areas will also be used to assess effectiveness of the materials s

- The primary objective is to determine effectiveness of the educational materials through questions measuring :
  - The level of knowledge and understanding regarding key content areas of the educational materials including:
    - Evaluation of home infusion (HCP)
    - Elements to address when training the patient/caregiver
    - Actions to be taken in case of an adverse event
  - Implementation of the logbook (owned by the patient but reviewed by the HCP)

8 RESEARCH METHODS

8.1 STUDY DESIGN

The study design is a cross-sectional self-administered online survey conducted independently in two populations: 1) HCPs and 2) Patients or their caregivers

8.1.1 HCP recruitment

HCPs include both physicians and nurses.

A) Physicians: A target list of physicians known to be prescribing Fabrazyme home infusion will be provided by the MAH and used for recruitment. Potentially eligible physicians will be approached via telephone or email with information about this study. The method of contacting physicians is dependent on contact details provided in the target list.

B) Nurses: Based on information provided by the MAH, Nurses play an important role in providing in person medical supervision and education to patients receiving Fabrazyme home infusion in the UK, France, Italy and Finland. Therefore nurses will be included in the HCP sample in these markets. To recruit nurses we will use a mix of both targeted recruitment and via physician referral; for targeted recruitment the MAH will provide a list of external home care provider companies with contact details per market. Potentially eligible nurses will be contacted via telephone or email with information about this study. The method of contacting nurses is dependent on contact details obtained via the physicians or home care providers.

To increase participation in the survey all HCPs on the target lists will be sent a letter of endorsement from the MAH and MAH representative that provides information to validate the regulatory requirement associated with the reason for the survey. Interested HCPs will be asked screening questions to check eligibility for the survey.

Inclusion/exclusion criteria:

- Involved in the treatment of at least 1 patient with Fabry disease in the last 12 months
- Have prescribed Fabrazyme for home infusion and/or monitor, oversee the management, and/or provide in person medical supervision of patients on Fabrazyme home infusion in the last 12 months
- Not a current or ex-employee of Sanofi

If the criteria are met, HCPs are asked to provide consent to participate in the study. Once consent has been provided HCPs is provided with a link to access and complete the main survey.

8.1.2 Patient/caregivers recruitment

All HCPs from the target lists provided by the MAH and who are contacted regarding the study will also be asked to refer all patients they are treating for Fabry disease for inclusion within the study.

HCPs send an invitation letter to all potentially eligible patients. The invitation letter will be pre-drafted by the MAH and MAH representative and will contain rationale for the research, overview of length and type of survey and contact details.

Interested patients and/or their caregivers respond to the invitation letter. Patients and/or caregivers are screened for eligibility, if criteria are met, they are asked to provide consent to participate in the study.

Patient/Caregiver inclusion/exclusion criteria include

- Diagnosed with Fabry disease / caring for a patient diagnosed with Fabry disease
- Patient received Fabrazyme in the home infusion setting in the past 12 months
- Not a current or ex-employee of Sanofi

Eligible patients / caregivers who provide consent to take part in the study will be provided with a link to access and complete the main patient survey. Only one patient or caregiver will be permitted to complete the survey per household.

8.2 SETTING

The surveys will be conducted in 5 countries (France, UK, Italy, Finland and Norway). Table 1 below shows the home infusion patient and prescriber numbers for the 10 markets in which Fabrazyme home infusion is most prevalent as provided by MAH.

Table 1 - Approximate number of patients and prescribers for top 10 countries based on data provided by the MAH, as of February 2017

Country	Potential home infusion prescribers	Fabrazyme home infusion patients
France	30	140
UK	20	190
Italy	10	65
Finland	15	27
Norway	8	34
Germany	5	7
Spain	1	1
Netherlands	1	35
Sweden	3	10

Country	Potential home infusion prescribers	Fabrazyme home infusion patients
Belgium	5	10
TOTAL	98	519

The countries selected for this study had the highest number of prescribers of Fabrazyme home infusion or patients receiving Fabrazyme in the home setting based on the data in table 1. There are:

- 98 prescribers of Fabrazyme home infusion and 83 of these (85%) were based in France, UK, Italy, Finland and Norway.
- 519 Fabrazyme home infusion patients and 456 of these (88%) were based in France, UK, Italy, Finland and Norway.

Other markets (Germany, Spain, Netherlands, Sweden and Belgium) only had a maximum of 5 prescribers of Fabrazyme home infusion.

8.3 VARIABLES

The HCP and patient surveys will be comprised of

A) Screening section for eligibility and demographics

B) Main questionnaire for eligible subjects.

These items and the variables collected are described in detail in sections 8.3.1 to 8.3.4.

8.3.1 HCP screener

Screener data will be entered into the online survey link either by a member of the local fieldwork agency, asking the HCP screening questions over the phone, or independently by the HCP via the online link. All data entered will be captured on the online server to be downloaded at the end of fieldwork.

Table 2 - Overview of HCP screening questions*

Section	Content
Section 1	Survey introduction

Section	Content
Section 2	Demographics and screening questions • Specialty • Years of experience treating Fabry disease • Years of experience prescribing Fabrazyme home infusion • Practice setting • Hospital type • Fabry disease patient workload (# patients seen in last 1 year) • Personal responsibility to prescribe Fabrazyme

*Content included, but not limited to the items included in the table

8.3.2 HCP Survey Questionnaire

Upon informed consent from the HCP, eligible HCPs will be provided a link to access and complete the main survey. Data will be entered online independently by the HCP. All data entered will be captured on the online server to be downloaded at the end of fieldwork.

Table 3 - Overview of HCP main survey questions*

Section	Content
Section 1	Key performance indicators • Awareness of materials • Which materials have been received • Have materials been read • Overall usefulness rating of materials • Comprehensiveness of the key sections in education materials • Sources of information for home infusion
Section 2	Evaluation for home infusion and training • Use of materials to evaluate and select patients for home infusion • Criteria required for a patient to be deemed eligible (knowledge assessment) • Are patients trained on home infusion process • Use of materials for training on home infusion process • Frequency key areas are covered in training • Steps taken in case of IAR (knowledge assessment) • Frequency of reviewing patients home infusion administration • Helpfulness of materials when reviewing home infusion administration

Section	Content
Section 3	Implementation of the logbook • Frequency of completing administration details in logbook • Frequency of reviewing patients logbook • Was patient trained on logbook • Frequency of documenting changes, checking infusion rate and dose administered in logbook • Frequency logbook is discussed with patient/caregiver • Action taken if IARs recorded in Logbook • Key responsibilities of physician

*content included, but not limited to items in table

8.3.3 Patient screener

Screener data will be entered into the online survey link either by a member of the local fieldwork agency, asking the patient screening questions over the phone, or independently by the patient via the online link. All data entered will be captured on the online server to be downloaded at the end of fieldwork.

Table 4 - Overview of patient screening questions*

Section	Content
Section 1	Survey introduction
Section 2	Demographics and screening questions • Patient or caregiver completing survey • Age of patient • Setting in which Fabrazyme administered (home infusion vs hospital setting)

*Content included, but not limited to the items included in the table

8.3.4 Patient Survey Questionnaire

Upon informed consent from the patient, eligible patients will be passed a link to access and complete the main survey. Data will be entered online independently by the patient. All data entered will be captured on the online server to be downloaded at the end of fieldwork.

Table 5 - Overview of patient main survey questions*

Section	Content
Section 1	Key performance indicators • Materials provided by physician • Which materials were received • Have materials been read • Involvement of infusion nurse or other medical trained professional • Frequency in which materials are referenced
Section 2	Understanding and knowledge of educational materials • Overall usefulness rating of materials • Ease of understanding of the key sections in education materials • Knowledge assessment of preparation, administration and storage of Fabrazyme • Frequency key preparation and administration steps conducted
Section 3	Implementation of the logbook and handling AR • Frequency in which logbook is completed and taken to appointments • Frequency Infusion changes reported in logbook • Familiarity with side effects/risks associated with home infusion • Sources of information for learning about side effects/risks • Action taken in case of AR (knowledge assessment) • Reporting side effects in logbook • Frequency logbook discussed with physician • Usefulness of logbook • Sources of information for home infusion

*content included, but not limited to items in table

8.4 DATA SOURCES

Data sources will include:

- HCP materials: Screener, Self administered online Survey questionnaire

Patient materials: Screener, Self administered online Survey questionnaire

The online interview is estimated to take approximately 10-15 minutes to complete. All data entered into the survey will be collected onto an online server.

8.5 STUDY SIZE

8.5.1 HCP sample size

Given the rarity of Fabry disease and the small prescriber and patient universe for Fabrazyme (agalsidase beta) home infusion as demonstrated in Table 1 in Section '8.2 Setting' we are limited in terms of sample sizes that we can feasibly achieve.

A total sample size of 34 HCPs (physicians and nurses) who prescribe, monitor, oversee the management, and/or provide in person medical supervision of patients on Fabrazyme home infusion will be recruited across key countries previously described in '8.2 Setting'. A minimum of 25 physicians will contribute to the overall HCP sample.

The sample size calculation is based on several factors/assumptions:

- Total number of eligible respondents (assumed to be n=83 based on Table 1)
- Assumption that the target list is high quality and contains up to date contact information and that all respondents have given consent to be contacted by a 3rd party (due to GDPR regulations coming in place in May 2018)
- Assumption of a response rate of 30-40% based on previous experience in recruiting via target list in similar therapy area
    - Example 1 – French study in Gaucher disease – 30-40 respondents were contacted to achieve 15 completes (38-50% response rate)
    - Example 2 – Italian study in Gaucher disease – 65 eligible respondents were contacted to achieve 13 completes (20% response rate)

Given ~83 prescribing physicians across the 5 markets for consideration and a response rate of 30-40%, the maximum physicians expected to take part is therefore 25-34. This sample size reflects ~40% of prescribers across the 5 markets where Fabrazyme (agalsidase beta) home infusion is most prevalent.

In addition to the physicians, the HCP survey will include nurses who are involved in providing in person medical supervision of patients on Fabrazyme home infusion. There are not robust estimates of the numbers of nurses available for recruitment in each country, but we anticipate being able to recruit nurses through the methods outlined in section 8.1.1 in the UK, Italy, France and Finland, based on country-based direction. All markets will be investigated and final inclusion will be confirmed once successful contacts and acceptance to participate has been achieved.

Table 6 denotes the level of precision for a sample of 34 for a selection of response levels to a particular question

Table 6 - Precision estimates for the target HCP sample size (n=34) for 60, 70, and 80% correct response levels

Correct response percentage	Lower limit	Upper limit	Precision (+/-)
80%	66.6%	93.4%	13.4%
70%	54.6%	85.4%	15.4%
60%	43.5%	76.5%	16.5%

8.5.2 Patient sample size

A total sample size of 18 Patients and/or Caregivers will be recruited across key countries previously described in '8.2 setting'. Given the rarity of the patient universe we are targeting, the patient sample numbers included are driven primarily by feasibility.

Sample size feasibility the calculations were based on several factors/assumptions:

- Total number of eligible patients is assumed to be 456 based on France, UK, Italy, Finland and Norway data in Table 2
- The patient recruitment approach will be via HCP referrals
  - All HCPs contacted are asked to pass on details of the survey to eligible patients, however there is a higher likelihood that HCPs who participate will encourage their patients to also participate. Thus, most conservative patient reach estimate would be limited to the patients treated by these 34 HCPs (~40%) or 180 patients.
- Assumed that despite best efforts the patient response rate will be low based on:
  - Reliance on HCPs informing all Fabrazyme patients/caregivers of the study
  - Reliance of patients/caregivers in being proactive in responding to the invitation letters

Table 7describes the level of precision for a sample of 34 for a selection of response levels to a particular question.

Table 7 - Precision estimates for the target patient/caregiver sample size (n=18) for 60, 70, 80% correct response levels

Correct response percentage	Lower limit	Upper limit	Precision (+/-)
80%	61.5%	98.5%	18.5%
75%	55.0%	95.0%	20.0%
70%	48.8%	91.2%	21.2%
60%	37.4%	82.6%	22.6%

8.6 DATA MANAGEMENT

Participant answers to the online survey will be collected using Confirmit Horizons software and the data exported via SPSS (.sav) and analyzed using Q-Research Software. The data is stored in the EEA in London, England. The data is isolated on the server. The Confirmit Horizons SaaS (software as a service) hosting environments are not "cloud" based. Horizons SaaS hosting environments store the data physically in a specific datacenter, and the management of the datacenter is hosted by Rackspace. Rackspace holds the following security certifications, including ISO27001, Payment Card Industry (PCI DSS), ISO 9001, and is SOC II audited in accordance with SSAE16 / ISAE3402. In order to comply with General Data Protection Regulation (GDPR) only a minimum amount of personal data will be collected in order to fulfill the purposes of the survey. This data will be retained only for as long as the duration of the project. On Confirmit Horizons SaaS there is a 'countdown' feature whereby the project owner defines a retention period for the whole survey database. The data will be deleted from the Confirmit Horizons SaaS environment at that date. Prior to the deletion date, the system will send an e-mail reminding the project owner that the data will be deleted. Data rendered anonymous can be kept indefinitely and will be deleted upon instruction from the project owner.

8.7 DATA ANALYSIS

The analysis will be cross-sectional and descriptive. Categorical data will be summarized by counts and percentages. Continuous data will be summarized using number, median, minimum and maximum values. Missing data will be noted for each variable.

A **positive outcome** reported across key pre-defined questions for each of these objectives would support the effectiveness of the educational material. For this assessment, a positive outcome is defined as at >70% of the survey participants providing a 'correct' response (specific questions and responses are outlined in Tables Table 8 and Table 9). The 70% cut point is based on previous experience from other surveys evaluating the effectiveness of educational materials.

Table 8 - Questions to assess effectiveness in HCP survey

Category of assessment	Question text [Answer options]	Criteria for 'effective assessment'
To assess if materials are being received and read	A2. Which of the following material have you received or had access to? Select all that apply 1. Summary of Product Characteristics (SMPC) 2. Fabrazyme Home Infusion Therapy: A guide for Healthcare professionals treating patients with Fabry disease 3. Fabrazyme Home Infusion Therapy: Manual for Patients with Fabry disease who receive home infusion of Fabrazyme 4. None of the above	Majority of HCPs selecting Code 2
	A3. Have you read the Fabrazyme (agalsidase beta) home infusion educational materials? 1. Yes 2. No	Majority of HCPs selecting Code 1
To assess evaluation of home infusion	B1. Do you use the educational materials to evaluate and select patients for home infusions? 1. Yes 2. No	Majority of HCPs selecting Code 1
	B2. Which of the following criteria must be fulfilled before a patient is deemed eligible for Fabrazyme (agalsidase beta) home infusion? Select all that apply 1. Patient must be medically stable 2. A comprehensive evaluation must be completed before deciding on transfer of therapy to home infusion 3. Patient must have received Fabrazyme infusions for several months in a controlled setting and previous infusions well tolerated 4. Don't know	Majority of HCPs selecting codes 1, 2 and 3
To assess level of training to patients/caregivers	B4. Do you use the Fabrazyme (agalsidase beta) home infusion educational materials when training the patient/caregiver on the home infusion process? 1. Yes 2. No	Majority of HCPs selecting Code 1
	B5. How frequently do you cover each of the following areas when training the patient/caregiver on Fabrazyme home infusion? [1. Always / 2. Regularly / 3. Rarely / 4. Never] a. Importance of adhering to the pre-defined infusion schedule (dose and infusion rate) b. Method of preparation, reconstitution and administration c. Instructions for handling Adverse Events (AEs) and Infusion Associated Reactions (IARs) d. Completing the logbook	Majority of HCPs selecting codes 1 & 2 for each area
To assess knowledge on actions taken in case of IAR and AE	B6. In the event of an infusion associated reaction (IAR) what are the appropriate steps that should be taken? Select all that apply 1. Infusion is immediately discontinued	Majority of HCPs selecting codes 1 & 3

	2. Infusion is completed and IAR recorded in the logbook 3. Patient/Infusion nurse to call the treating physician immediately 4. Don't Know	
To assess implementation of logbook	C1. How often do you clearly state the Fabrazyme (agalsidase beta) home infusion administration details in the logbook of your Fabry patients? [1. Always / 2. Regularly / 3. Rarely / 4. Never]	Majority of HCPs selecting codes 1 & 2
	C2. How often do you review your patients' logbooks? [1. Always / 2. Regularly / 3. Rarely / 4. Never]	Majority of HCPs selecting codes 1 & 2
	C4. Considering the logbook, how often do you do each of the following: [1. Always / 2. Regularly / 3. Rarely / 4. Never] a. Document changes to the infusion schedule b. Check the infusion rate c. Check the dose administered d. Discuss logbook with patient/caregiver	Majority of HCPs selecting codes 1 & 2 for each element

Table 9 - Questions to assess effectiveness in patients/caregivers survey

Category of assessment	Question text [Answer options]	Criteria for 'effective assessment'
To assess if materials are being received read and referred to	A2. Have you [or the person you care for] received any of the following? Select all that apply 1. Package leaflet for Fabrazyme 2. Fabrazyme Home Infusion Therapy: Manual for Patients with Fabry disease who receive home infusion of Fabrazyme 3. None of the above	Majority of patients selecting Code 2
	A3. Have you read the Fabrazyme (agalsidase beta) home infusion educational materials? 1. Yes 2. No	Majority of patients selecting Code 1
	A5. How often do you [or the patient] refer to the educational materials when the home infusions are being done? 1. At every infusion 2. Frequently 3. Rarely 4. Never	Majority of patients selecting Code 1 or 2
To assess knowledge on preparation of infusion	B3. Which of the following statements are true in relation to the preparation, administration and storage of Fabrazyme. Select all that apply 1. The vials must be removed from the refrigerator approximately 30 mins before preparation 2. The reconstituted mixture should be shaken up 3. The reconstituted solution must be clear and colourless before use	Majority of patients selecting Code 1, 3 & 4

	4. The tourniquet should be applied to identify a vein 5. The product can be stored at room temperature for 48 hours before use 6. None of the above are true 7. N/A I don't prepare the infusion on my own	
To assess knowledge on actions taken in case of AE	C5. What would you do if [you / the patient] developed a headache and a fever during the infusion? 1. Complete the infusion and then rest 2. Immediately stop the infusion 3. Contact the physician 4. Record details in the logbook 5. Don't Know	Majority of patients selecting Code 2, 3 and 4
To assess implementation of logbook	C1. Considering the Fabrazyme (agalsidase beta) home infusion, how often do you or the nurse who helps you with the infusion (if applicable) do the following actions? [1. Always / 2. Regularly / 3. Rarely / 4. Never] a. Fill out the infusion data in the logbook b. Take the logbook to each appointment with the prescribing physician	Majority of patients selecting codes 1 & 2 for both actions
	C2. How often do you or the nurse who helps you with the infusion report changes about the infusion (dose or infusion rate) in [your / the patient's] logbook? 1. Always 2. Regularly 3. Rarely 4. Never 5. N/A There have been no changes	Majority of patients selecting codes 1 or 2 (excluding those selecting code 5 from calculation)
	C6. If [you / the patient] had a side effect, should you report the side effect in your log book? 1. Yes, always 2. Only if I think it's serious 3. No, it is not necessary	Majority of patients selecting codes 1
	C7. How often do you review the logbook with [your / the patient's] physician? 1. Always 2. Regularly 3. Rarely 4. Never	Majority of patients selecting codes 1 or 2

8.8 QUALITY CONTROL

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

8.8.1 Data quality management

To ensure the validity of the results, it is necessary to ensure that the data collected are of good quality. This implies minimizing any missing data and ensuring the data collected is accurate. To maximize data quality, the following procedures will be undertaken:

1. Adelphi will thoroughly brief local fieldwork agencies, detailing study objectives, physician inclusion criteria and other logistical aspects of the study. Adelphi will also carry out regular follow-up by telephone/email to ensure the physician screening and recruitment is being executed correctly.
2. Both the screener and questionnaire will be carefully designed to contain clear respondent instructions at each question.
3. The survey will primarily consist of questions that include a list of predefined answers for participants to select from when making their responses.
4. Logic checks will be programmed in the internet script to define expected ranges/answers, based on research team's experience and therapeutic knowledge. The online link will also contain "live" checks and error messages to prompt the physician to check missing data and illogical answers whilst they are completing the survey.

   4.1 All logic checks are specified in the data collection materials that are supplied; the script writer programs the logic checks and the research team checks that the logic is implemented before fieldwork.
5. The patient/caregiver survey will be piloted by 1 patient/caregiver per country in advance of main fieldwork to check the design and language used in the survey is understandable and that all survey logic is implemented.

   5.1 The patient/caregiver will complete the online survey and then participate in a telephone debrief with a research team member commenting on any issues in the survey.

   5.2 Research team member will review the data downloaded from the survey to ensure all logic is correct.

   5.3 Any changes suggested will be recorded in an 'internet checking log' and the scriptwriter indicates whether and when each change is actioned.

   5.4 This is incorporated into the patient survey prior to main fieldwork.

   5.5 To ensure we do not jeopardize patient recruitment we will target a patient with a similar condition to Fabry for doing the pilot interview.
6. The survey will be soft-launched. 1 HCP and 1 patient/caregiver in each country will be fielded before full launch of fieldwork. This will check that the design of the questionnaire works in practice.

   6.1 The respondents complete the online survey

6.2 Research team member will review the data downloaded from the survey to ensure all logic is correct.

6.3 Any errors found will be recorded in the 'internet checking log' and the scriptwriter indicates whether and when the change is actioned.

6.4 Changes are then tested by the researcher and uploaded to the main survey link for main fieldwork.

6.5 Adelphi will perform quality control checks once in field to ensure data integrity and will follow quality control guidance. Checks include: repeated response patterns, straight-lined responses through rating scale questions and high speed completion of survey (See appendix for Data quality control document)

6.5.1 Data is downloaded, checked and flagged in fieldwork monitoring report that is sent to researchers daily.

6.5.2 Research team review the flagged respondents and exclude the respondent data if the data is suspect.

6.5.3 Fieldwork agency is notified that this respondent will need to be replaced and reason for exclusion.

7. All data collection material will be translated to the required languages by selected agencies / approved translators. Translated materials will be sent to members of the freelance proof-reader team, who will check the final translated web interface for accuracy.

8.8.2 Data recording and document retention

All documents will be filed to structured computer network folders and these files rather than paper copies are regarded as key project records.

All key documents produced as part of project work including proposals, data collection material, code frames (i.e. a defined list of attributes derived from answers to each open ended question, used as basis to measure the frequency of recall of these attributes) by the frequency of which and for reporting include version/revision numbering to a standard format.

On completion of the project, data collection records and any documents relating to the project not held as computer files, will be collated and prepared for archiving by the Research Team with records kept of the archives held.

Archived records will retained for a minimum of five years before secure destruction. Some archived records may be kept longer, depending on the type of material and Client instructions. The archive packs show retention periods.

All computer files will be retained for an indefinite period (including archived files).

All electronic data files will be de-identified and stored in password protected computers. Response data from all interviews for each participating respondent will be linked through an assigned unique study identification number.

8.9 LIMITATIONS OF THE RESEACH METHODS

The following section briefly describes potential limitations of the study and its design. These include:

- While best efforts will be made to recruit a relatively large proportion (~40%) of the eligible population of HCPs, it remains a small and finite population and we cannot be fully confident in representativeness.
- Patients/caregivers will be recruited via HCP referrals, there may be an element of HCP selection bias that takes place despite request for HCPs to refer all Fabrazyme home infusion patients making the population less generalizable. In addition, the types of patients who agree to participate may not be completely generalizable to the entire patient population.

To minimize the risk of bias from participating physicians the MAH will

- Contact all HCPs on the target list to recruit for patients (regardless of whether they take part themselves).
- Not ask that physicians have received the materials or that patients need to have received the materials upon recruitment
- Explain the purpose of the survey from a regulatory purpose in the invitation letter and not specifically mention it is to assess the education materials.

It is not possible to collect data on HCPs who decline participation, thus comparisons between participating with non-participating HCPs is not possible.

- The sample size is based on assumptions from previous experience with recruiting HCP and patients from similar surveys. However, despite best efforts for recruitment, the maximum sample size may not be achievable given the limited universe of potentially eligible providers and patients due to the fact that Fabry disease is rare and the number of patients on home infusion is further limited.
    - A full record of recruitment progress will be kept, including the number of respondents targeted, number of times contacted, reason for no participation, number of completes.

8.10 OTHER ASPECTS

Not applicable

9 PROTECTION OF HUMAN SUBJECTS

The online survey will include text to comply with current legislation and industry guidelines regarding Adverse Events and informed consent. Respondent's right to privacy and protection of their personal data will be respected and identifying information such as a respondent's name, email address, home address or phone number will not be recorded.

The industry guidelines and legislation will be:

- European Federation of Pharmaceutical Industries and Associations (EFPIA) Code on the Promotion of Prescription-Only Medicines to, and Interactions with, Healthcare Professionals 2014
- EU Data Protection Directive 11995,
- EU Directive on Privacy and Electronic Communications (2002/58/EC) 2003
- EFPIA Code on Disclosure of Transfers of Value from the Pharmaceutical Companies to Healthcare Professionals and Healthcare Organisations 2014.

After the respondent consent has been signed, a unique link with password will be sent out to the respondents for them to complete the survey. This will ensure that respondents' identities are validated.

There will be no audio or video recording during any point of the study procedures. If an Adverse Event is reported then consent will be obtained to follow up for contact details after informing the respondent about the purpose of data collection and processing of personal data.

10 MANAGEMENT OF REPORTING ADVERSE EVENTS/ADVERSE REACTIONS

This study is not designed to collect information on individual adverse drug reactions (ADR) associated with the use of Fabrazyme or any Sanofi product. However, it is possible that, during the conduct of the surveys, respondents may spontaneously provide information that meets the criteria for an ADR.

If during the course of the study Adelphi becomes aware of any adverse drug reactions regarding any Sanofi product, it shall be reported to the competent Sanofi pharmacovigilance (PV) department within one business day from the date of Adelphi becoming aware of such data by:

- completing the PV Reporting Form
- and sending it to the local Sanofi PV department

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

11 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

11.1 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.

11.2 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 home infusion education materials, results should be interpreted in combination with the evaluation of safety and clinical outcomes.

12 REFERENCES

None

13 APPENDICES

Appendix 1. HCP Survey

Appendix 2. Patient Survey