STUDY PROTOCOL

Study title	A multi-country time and motion study to describe the experience of clinicians, patients and their caregivers during the treatment of Fabry Disease with Enzyme Replacement Therapy with agalsidase alfa and agalsidase beta
Short title	A study to describe the experience of both patients and their clinicians in the treatment of Fabry Disease with Enzyme Replacement Therapy.
Study Sponsor	Amicus Therapeutics
Key Sponsor contact	[redacted] Associate Director Global Market Access [redacted] [redacted]
Study Management Company	Open Health The Weighbridge, Brewery Courtyard High Street Marlow, SL7 2FF
Country(-ies) of study	Taiwan, Turkey, Brazil, and Japan
Protocol version	Final V4
Date	23 March 2020

Confidentiality Notice

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This document must not be disclosed to anyone other than the study staff and members of the local competent authority and independent ethics committee.

The information in this document cannot be used for any purpose other than the evaluation or conduct of the study without the prior written consent of Open Health and Amicus Therapeutics.

APPROVAL SIGNATURE PAGE

On behalf of the sponsor, Amicus Therapeutics:

NAME:	[redacted]
TITLE:	Executive Director, Global Medical Lead, Fabry Disease
SIGNATURE:	[redacted]
DATE:	

NAME:	[redacted]
TITLE:	Associate Director, Global Market Access
SIGNATURE:	[redacted]
DATE:	12 May 2020 | 4:21 PM BST

INVESTIGATOR APPROVAL SIGNATURE PAGE

On behalf of the Principal Investigator at each site:

I have carefully read this protocol entitled **"**A multi-country time and motion study to describe the experience of clinicians, patients and their caregivers during the treatment of Fabry Disease with Enzyme Replacement Therapy with agalsidase alfa and agalsidase beta**",** and agree that it contains all the necessary information required to conduct the study. I agree to conduct this study as outlined in the protocol.

NAME:	
TITLE:	
SIGNATURE:	
DATE:	

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1. List of abbreviations

Abbreviation	Definition
ADR	Adverse Drug Reaction
AE	Adverse event
CFR	Code of Federal Regulations
CI	Confidence interval
CNS	Central nervous system
CRA	Clinical Research Associate
CRF	Case report form
CRO	Clinical Research Organisation
CSI	Caregiver Strain Index
DMP	Data management plan
eCRF	Electronic case report form
EDC	Electronic data capture
EEA	European Economic Area
eGFR	Estimated glomerular filtration rate
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ERT	Enzyme replacement therapy
EU	European Union
FD	Fabry Disease
FDA	Food and Drug Administration
Gb3	Globotriaosylceramide
GDPR	General Data Protection Regulation
GI	Gastrointestinal
GVP	Good Pharmacovigilance Practice
HCP	Healthcare Professional
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
IEC	Independent ethics committee

IQR	Interquartile range
IRB	Institutional review board
ISPE	International Society for Pharmacoepidemiology
IV	Intravenous
LOE	Lack of Effect
LVMi	left ventricular mass index
MI	Myocardial infarction
MRI	Magnetic Resonance Imaging
PC	Product Complaint
PQC	Product quality complaint
SAP	Statistical analysis plan
SD	Standard deviation
SF-12	12 Item Short Form Survey
SF-36	36 Item Short Form Survey
SS	Special Situations
STROBE	Strengthening the reporting of observational studies in epidemiology
TIA	Transient ischaemic attack
WBC	White Blood Cell
WHO-5	World Health Organization-5 Wellbeing Index
WPAI	Work Productivity and Activity Index
WPAI-CG	Work Productivity and Activity Index: Caregiver

2. Key definitions

Episode of care: An episode of care is an element or part of the care or treatment pathway which is being studied or measured. For the purpose of this study, an episode of care will constitute all healthcare professional (HCP) activities involved in the preparation and administration of a single dose of enzyme replacement therapy (ERT) with agalsidase alfa and agalsidase beta, including ERT (and pre-medication) preparation, pre- and post-administration assessment, pharmacy and clinic activities, and any follow up activities.

Caregiver: in the context of this study a caregiver is defined as an individual aged 18 years or over who has a personal relationship with and provides informal (unpaid) care, support or assistance to someone diagnosed with Fabry Disease, and accompanies them to the hospital or treatment centre for ERT administration on one or more occasion during the study data collection period. For example, this may be a parent, spouse/ partner, son/ daughter, other relative, neighbour or friend.

3. Responsible parties

The names, titles, degrees, addresses and affiliations of all responsible parties, including the Principal Investigators, co-investigators, and a list of all participating centres, Study Management Company and Sponsor contacts will be maintained in a separate document.

4. Abstract

Title	A multi-country time and motion study to describe the experience of clinicians, patients and their caregivers during the treatment of Fabry Disease with Enzyme Replacement Therapy with agalsidase alfa and agalsidase beta
Rationale for study	Enzyme replacement therapy (ERT) with agalsidase alfa (Replagal®, Shire or biosimilar) or agalsidase beta (Fabrazyme®, Sanofi Genzyme or biosimilar) is the current mainstay of treatment for patients with Fabry Disease (FD). Both ERT preparations need to be administered as an intravenous (IV) infusion every two weeks. Migalastat (Galafold®, Amicus Therapeutics), an orally-administered treatment for patients with FD with amenable mutations, is now approved in a number of countries. As oral therapies for FD become available, there is a need for comprehensive information about the burden of current treatments from the perspective of both patients and their caregivers and healthcare providers, to enable them to make fully informed decisions about the most appropriate treatment strategy. There is currently a paucity of data on the true resource burden associated with use of existing ERT and the wider impact of attendance for ERT on health-related quality of life (HRQoL) and work productivity. The present study will address these evidence gaps by generating robust real world data to quantify the current burden of ERT for the treatment of FD across four countries. The study will utilise a time and motion methodology to measure the total healthcare professional (HCP) time associated with a single episode of ERT administration, with patient- and caregiver-reported outcomes including HRQoL, wellbeing, levels of fatigue, work productivity and the strain of providing care, to be collected directly from patients with FD and their caregivers. The data may be utilised by Amicus Therapeutics in submissions to Health Technology Assessment (HTA) bodies, and will

	be useful for HCPs to inform future treatment decisions and ongoing patient management.
Research question and hypothesis	What is the total HCP time associated with the preparation and administration of a single dose of ERT in patients with FD and the patient and caregiver time and costs associated with an ERT attendance? What is the impact of FD on patients' HRQoL, wellbeing, levels of fatigue and work productivity? What is the burden of care provision for the caregivers of patients with FD and the impact on their work productivity? This is a descriptive study and there is no *a priori* hypothesis to be tested.
Objectives	**Primary objective** To quantify the total time spent by HCPs in the preparation and administration of a single dose of ERT (with agalsidase alfa and agalsidase beta) in patients with FD. **Secondary objectives** 1. To quantify the total patient time, costs (i.e. out of pocket expenses) and work-related absence associated with attendances for the administration of a single dose of ERT (with agalsidase alfa and agalsidase beta) in patients with FD. 2. To quantify the total caregiver time, costs (i.e. out of pocket expenses) and work-related absence associated with accompanying a patient with FD for the administration of a single dose of ERT (with agalsidase alfa or agalsidase beta). 3. To describe patient-reported HRQoL (measured by the 12 Item Short Form Survey [SF-12]), wellbeing (measured by the World Health Organization-5 Wellbeing Index [WHO-5]), levels of fatigue (measured by a bespoke Fatigue Likert scale) and work productivity (measured by the Work Productivity and Activity Index [WPAI] questionnaire) in patients with FD treated with ERT. 4. To describe work productivity (measured by the WPAI for caregivers [WPAI:CG]) and the strain of care provision (measured

	by the Caregiver Strain Index [CSI]) in caregivers of patients with FD treated with ERT.
Study design	This is an international, non-interventional research study of adult patients with FD and their caregivers. The study will comprise a prospective time and motion evaluation and a cross-sectional evaluation of patient and caregiver-reported outcomes. Patients' demographic characteristics will be collected from hospital medical records. For the cross-sectional evaluation of patient and caregiver-reported outcomes, patients with FD and their caregivers will be asked to complete a series of questionnaires, to include validated measures of HRQoL, wellbeing and work productivity (for patients) and work productivity and the strain of care provision (for caregivers). Patients and caregivers will also complete a bespoke questionnaire to evaluate the total time associated with attending the hospital or treatment centre for a single ERT administration visit, and time away from work. In addition, patients will also be asked about their level of fatigue using a bespoke Likert scale. With the exception of the work productivity questionnaire and Fatigue Likert scale, the study questionnaires will be completed at a single point in time, when the patient attends the hospital or treatment centre for administration of ERT. The work productivity questionnaire (which has a recall period of seven days, excluding the day of completion) will be completed twice; the first work productivity questionnaire will be completed 1-7 days after receiving a dose of ERT (ideally within 2 days), to capture a seven day period that includes an ERT administration visit and the second questionnaire will be completed on the day the patient attends the hospital or treatment centre to receive their next dose of ERT (to capture a seven day period that does not include ERT administration). The Fatigue Likert scale will be completed three times; during an ERT administration visit, on the evening of the visit and the next day.

	Separate patient consent will be obtained for the time and motion evaluation and for the cross-sectional evaluation of patient-reported HRQoL, wellbeing, levels of fatigue and work productivity; thus, patients who do not wish to complete the study questionnaires will remain eligible for the time and motion study (and vice versa), provided that consent has been obtained.
Setting	Patients with FD who are receiving ERT and their caregivers will be identified and recruited from approximately 12 specialist centres in four countries (Taiwan, Turkey, Brazil and Japan).
Participants	The target sample size for the time and motion evaluation undertaken as part of this study is 240 ERT episodes, including 60 ERT episodes (30 for agalsidase alfa and 30 for agalsidase beta) in each participating country. Ideally, a maximum of two ERT administration episodes will be observed per patient; as such, at least 30 patients are expected to be enrolled in each country. For countries with limited FD patient numbers, a review of episodes of care observed will be completed on an ongoing basis. It may be determined that it is possible to observe three episodes per patient in these circumstances, however only two episodes will be observed per patient wherever possible. For the questionnaire evaluation, approximately 120 patients and 20 caregivers will be expected to fill questionnaire sets (approximately 30 patients' and 5 caregivers' questionnaire sets per country). **Patient inclusion criteria** • Patients aged 18 years old or over at time of consent. • Patients with a documented diagnosis of FD. • Patients who have received ≥4 doses of ERT (with agalsidase alfa or agalsidase beta) for the treatment of FD. • Patients who present to the participating hospital(s) or treatment centre(s) for administration of a dose of ERT (as part of their routine treatment) during the data collection period.

	Patient exclusion criteria • Patients aged <18 years at time of consent • Patients who are unable or unwilling to give consent for study participation. • Patients whose ERT preparation and administration takes place exclusively in the home setting with no HCP involvement in preparation of the infusion. • *For the time and motion evaluation:* Patients whose ERT is administered by a HCP who does not consent to be observed. **Caregiver inclusion criteria:** • Aged 18 years of age or over at time of consent. • Self-identifies as a caregiver of a patient with FD for whom written informed consent has been obtained for inclusion in the study. **Caregiver exclusion criteria** • Caregiver (and/or the patient with FD whom they support or care for) is unable or unwilling to give consent for study participation. **Staff inclusion criteria (for time and motion study):** • Members of the whole care team responsible for administering agalsidase alfa and agalsidase beta to patients with FD. • Staff who have given written consent to be observed during the provision of care. **Participant selection** Consecutive eligible patients (and their caregivers) presenting at the participating centres during the prospective recruitment period will be included in the study until the required sample size (number of ERT episodes) is reached. For patients who are eligible to be observed more than once (for the time and motion study), initial consent for observation of up to three episodes of care will be obtained, and will be confirmed verbally by their HCP before the second episode of care.

	Each patient and caregiver will only be asked to complete one set of questionnaires (with the exception of the work productivity questionnaire [which will be completed twice] and the fatigue Likert questionnaire [which will be completed three times], as described above).
Data source(s)	Patients' demographic and clinical data will be sourced from patients' medical records and other systems within the main (specialist) participating FD centres and extracted into electronic case report forms (eCRFs). For the time and motion component of the study, prospective data relating to HCP time associated with the preparation and administration of a single dose of ERT will be captured by direct observation of HCPs by an independent external researcher or a member of the patients' care team, during the episode of care and recorded on a paper case report form (CRF) which will then be transcribed into an eCRF. Patient- and caregiver-reported outcomes will be reported directly by patients and caregivers using anonymised-coded paper-based questionnaires which will be transcribed into an Excel database by central data managers.
Study time period(s)	It is anticipated that the prospective recruitment / data collection period for this study will be approximately 4-5 months, starting from the date on which the relevant approvals to conduct the study are in place. A maximum of three episodes of care per patient during the data collection period will be included. Consenting patients with FD and their caregivers will be asked to complete the study questionnaires at the time points described above.
Study endpoints	Primary endpoint: Summary measures of the total time spent by HCPs in the preparation and administration of a single dose of ERT in patients

	with FD; stratified by country and by ERT product (agalsidase alfa or agalsidase beta). Main secondary endpoints: • Summary measures of the time spent by HCPs on each separate task associated with the preparation and administration of a single dose of ERT (with agalsidase alfa or agalsidase beta). • Summary measures of the total patient time and costs associated with attendance for the administration of a single dose of ERT (with agalsidase alfa or agalsidase beta). • Proportion of patients with work absence due to attendance for this ERT episode and number of hours absent. • Summary measures of the total caregiver time and costs associated with accompanying a patient with FD for the administration of a single dose of ERT (with agalsidase alfa or agalsidase beta). • Proportion of caregivers with work absence due to accompanying the patient for this ERT episode and number of hours absent. • Summary measures of patients': o HRQoL (SF-12 scores / responses). o General wellbeing (WHO-5 scores / responses). o Level of fatigue (Fatigue Likert scale) o Levels of work impairment (WPAI scores / responses). • Summary measures of caregivers': o Levels of work impairment (WPAI-CG scores / responses). o Level of strain in providing care for a patient with FD (CSI scores / responses).

5. Study amendments and updates

All amendments to the protocol will be documented in Table 1.

Protocol deviations will be documented in a Protocol Deviation Log (maintained in a separate document).

Table 1. Study amendments

Amendment number	Date of amendment	Section amended	Amendment description	Reason for amendment
1	Click here to enter a date.		None at present	
2	Click here to enter a date.			
3	Click here to enter a date.			
4	Click here to enter a date.			

6. Milestones

Table 2. Study milestones

Milestone	Planned date(s)/frequency
Planned regulatory approval activities	Start: Jun 2019 End: Aug 2020
Planned start of study (date of first consent)	Jun 2020
Planned collection of first data point	Jun 2020
Planned collection of last data point	Nov 2020
Study progress report 1	No progress report is planned
Interim study report 1	No interim analysis is planned
Registration in EU Post-authorisation study Register or equivalent public database	Clinical trials.gov; Feb 2020
Final report of study results (end of study)	Apr 2021

7. Rationale and background

Fabry disease (FD) is a rare inherited lysosomal disorder caused by deficiency or dysfunction of the enzyme α-galactosidase A, which leads to an accumulation of globotriaosylceramide (Gb3) within the lysosomes of many cell types leading to cellular dysfunction and multi-organ disease[1]. FD is associated with a number of characteristic clinical signs and symptoms including neuropathic pain, gastrointestinal complications, headaches, impaired sweating, vertigo, hearing impairment, angiokeratomas and cornea verticillata[2]. Over time, FD can lead to irreversible organ damage and is a cause of premature renal failure, heart disease, cerebrovascular events and death[3]. As X-linked disorder, male sufferers of FD tend to be more severely affected than females[4]. Patients with FD are widely reported to have reduced health related quality of life (HRQoL) compared with the general population[5,6] due to the debilitating symptoms and damage to vital organs. Increasing age, classical FD phenotype, more severe disease and pain have been identified as major contributors to reduced HRQoL[6].

Enzyme replacement therapies (ERT) with agalsidase alfa (Replagal®, Shire) and with agalsidase beta (Fabrazyme®, Sanofi Genzyme) currently represent two treatment options for patients with FD and have been shown to reduce substrate levels in several cell types. In addition there are reports of reductions in the severity of neuropathic pain, stabilization of renal and cardiac function and delay in the occurrence of serious complications[7–10]. However, both ERT preparations need to be administered as an intravenous (IV) infusion every two weeks and therefore lifelong ERT places a considerable burden on patients, their caregivers and healthcare services. ERT administered in the hospital or clinic setting requires frequent visits for IV infusions, which many patients find stressful and inconvenient; furthermore, hospital-based treatment often takes place in a specialist FD centre, which may be a considerable distance from the patient's home[11,12]. In some countries ERT can be administered in the patient's home under certain circumstances (for example, if the patient has stable disease and experienced no adverse reactions during hospital-based infusion) and this is generally perceived to be more convenient than hospital-based therapy[11–13], can improve treatment compliance[14] and may help to reduce the burden on healthcare services. However, even home-based ERT administration can cause disruption to a patient's daily activities and usually requires a healthcare professional (HCP) to supervise the infusion. To mitigate risk of adverse effects associated with ERT, patients are also frequently administered pre-medications with antihistamines and low-dose corticosteroids, which can be an added burden to patients.

Therapeutic options for FD have expanded over the past few years, with the development of orally-administered medicines such as Migalastat (Galafold®, Amicus Therapeutics) which has received regulatory approval in several countries. In this context, there is a need for comprehensive information about the burden of standard-of-care ERT treatments from the perspective of both patients and their caregivers and healthcare providers, to enable them to make fully informed decisions about the most appropriate treatment strategy. There is currently a paucity of data on the true resource burden associated with use of existing ERT and the wider impact of attendance for ERT on HRQoL and work productivity. Although data are available about the overall frequency and cost of ERT attendances[15,16], there have been no published data on the total time and cost involved for patients, caregivers and HCPs. In

addition, the impact of receiving ERT on work productivity has been described in market research[17] and qualitative research[18] but has not been formally quantified.

The present study will address these evidence gaps by generating robust real world data to quantify the current burden of ERT for the treatment of FD across four countries. The study will utilize a time and motion methodology to measure the total HCP time associated with an episode of ERT administration, with patient- and caregiver-reported outcomes including HRQoL, wellbeing, work productivity and caregiver strain, to be collected directly from patients with FD and their caregivers. The data may be utilized by Amicus Therapeutics in submissions to Health Technology Assessment (HTA) bodies, and will be useful for HCPs to inform future treatment decisions and ongoing patient management.

8. Research questions and objectives

8.1 Research questions

What is the total HCP time associated with the preparation and administration of a single dose of ERT in patients with FD and the patient and caregiver time and costs (out-of-pocket expenses) associated with an ERT attendance? What is the impact of FD on patients' HRQoL, wellbeing, levels of fatigue and work productivity? What is the burden of care provision for the caregivers of patients with FD and the impact on their work productivity?

8.2 Hypothesis

This is a descriptive study and there is no *a priori* hypothesis to be tested.

8.3 Primary objective

To quantify the total time spent by HCPs in the preparation and administration of a single dose of ERT (with agalsidase alfa and agalsidase beta) in patients with FD.

8.4 Secondary objectives

- To quantify the total patient time, costs (i.e. out of pocket expenses) and work-related absence associated with attendances for the administration of a single dose of ERT (with agalsidase alfa and agalsidase beta) in patients with FD.

- To quantify the total caregiver time, costs (i.e. out of pocket expenses) and work-related absence associated with accompanying a patient with FD for the administration of a single dose of ERT (with agalsidase alfa or agalsidase beta).
- To describe patient-reported HRQoL (measured by the 12 Item Short Form Survey [SF-12]), wellbeing (measured by the World Health Organization-5 Wellbeing Index [WHO-5]), levels of fatigue (measured by a bespoke Fatigue Likert scale) and work productivity (measured by the Work Productivity and Activity Index [WPAI] questionnaire) in patients with FD treated with ERT.
- To describe work productivity (measured by the WPAI-CG) and the strain of care provision (measured by the Caregiver Strain Index [CSI]) in caregivers of patients with FD treated with ERT.

9. Research methods

This study has been designed and will be conducted according to the requirements of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP; http://www.encepp.eu/index.shtml) and International Society for Pharmacoepidemiology (ISPE; https://www.pharmacoepi.org/resources/guidelines_08027.cfm) guidance, as appropriate.

9.1 Study design

This is an international, non-interventional research study of adult patients with FD and their caregivers. The study will comprise a prospective time and motion evaluation and a cross-sectional evaluation of patient- and caregiver-reported outcomes (including HRQoL, wellbeing, levels of fatigue and work-productivity [for patients with FD]; work productivity and the strain of care provision [for caregivers]). Patients' demographic characteristics will be collected from hospital medical records. No changes to routine patient management will be made for the purposes of any part of this study and there is no requirement for additional visits or investigations.

Separate patient consent will be obtained for the time and motion evaluation and the cross-sectional evaluation of patient-reported HRQoL, wellbeing, levels of fatigue and work productivity; thus, patients who do not wish to complete the study questionnaires will remain

eligible for the time and motion study (and vice versa), provided that consent has been obtained. Caregivers will consent to completion of the study questionnaires.

A prospective design for collection of patient-centred outcomes data was selected since it is unlikely that these will be documented in medical records. A prospective design is the only appropriate method for collecting time and motion and caregiver-reported outcomes data.

Based on the rarity of FD, the broad eligibility criteria and the number and types of participating centres, the results of this study should be generalisable to the wider patient population with FD treated with ERT with agalsidase alfa or agalsidase beta in routine clinical practice in the participating countries.

9.1.1 Prospective time and motion study

Patients with FD attending the hospital or treatment centre for administration of a single dose of ERT (with agalsidase alfa or agalsidase beta) during the prospective recruitment period will be observed by an independent researcher or a member of their care team for the duration of their episode of care. The observer will record the HCP time associated with all activities relating to the preparation and administration of ERT (including the pre-infusion clinical assessment and post-administration documentation). It is possible that a single patient may present to the hospital or treatment centre for administration of ERT multiple times within the recruitment period (when they return for follow-up treatment), but repeated observation of the same patient will ideally be capped at two episodes of care per patient, to minimise bias from multiple observations of patients with atypical resource use. For countries with limited FD patient numbers, a review of episodes of care observed will be completed on an ongoing basis. It may be determined that it is possible to observe three episodes per patient in these circumstances, however only two episodes will be observed per patient wherever possible. For patients who are eligible to be observed more than once, initial consent for observation of up to three episodes of care will be obtained, and will be confirmed verbally by their HCP before the second or third episode of care is observed.

9.1.2 Cross sectional evaluation of patient- and caregiver-reported outcome measures

Patients with FD and their caregivers will be asked to complete a series of questionnaires, to include validated measures of HRQoL, wellbeing and work productivity (for patients); and work productivity and the strain of care provision (for caregivers).

Questionnaires were selected based on their ease of use, short time required for completion (in order to minimise the burden on patients), availability in the required languages, and the fact that they have been previously validated in a similar context to our study:

- HRQoL will be assessed using the SF-12 version 2. The SF-12 is a shorter version of the 36 item Short Form Survey (SF-36) that uses 12 questions to measure functional health and wellbeing from the patients' point of view. It is made up of 8 domains: physical functioning, bodily pain, general health, vitality, physical role, role emotional, social functioning and mental health[19]. These 8 domains form 2 subscales: physical component summary and mental component summary. The SF-12 was chosen for the present study as it was used in a recent registry of patients with FD[20] and is less burdensome for patients to complete than the longer SF-36. It has a short completion time (approximately 5 minutes) and is available in all 4 languages of the study countries.
- Patients' general wellbeing will be assessed using the WHO-5[22]. It consists of 5 items and the timeframe for responses is based on the previous 2 weeks. The 5 items relate to feeling cheerful, calm, active, rested and being interested in life. The WHO-5 was selected to assess the impact of FD and its treatment on patients' well-being. It is quick and easy to complete (<5 minutes) and score.
- The impact of FD on patients' work lives will be assessed using the WPAI. The WPAI consists of 6 items. The WPAI was chosen for the present study as it is quick to complete (<5 minutes) and is available in all 4 languages of the countries selected in this study.

Caregiver-reported outcomes will be evaluated using the following validated questionnaires addressing work productivity and the strain of care provision:

- The impact of caring for a patient with FD on caregivers' work lives will be assessed using the WPAI specific to caregivers (WPAI:CG)[24]. The WPAI:CG consists of 6 items and was chosen for the present study as it is quick to complete (<5 minutes) and is available in all 4 languages of the study countries.

- The strain of providing care for a patient with FD will be assessed using the CSI. The CSI consists of 13 items and measures the strain of care provision in five domains (financial, physical, psychological, social and personal)[23]. It takes approximately 5 minutes to complete.

Patients and caregivers will also complete a bespoke questionnaire to evaluate the total time associated with attending the hospital or treatment centre for a single ERT administration visit, costs (i.e. out of pocket expenses) and time away from work. In addition, patients will also be asked about their levels of fatigue using a single-item bespoke Likert scale. Bespoke questionnaires will be designed specifically for the purpose of the study.

It is estimated that it will take approximately 25-30 minutes in total for patients to complete their questionnaires (including the second WPAI) and 15-20 minutes for caregivers to complete their questionnaires (including the second WPAI:CG).

Patient questionnaires will be presented in the following order: bespoke Fatigue Likert scale (first completion), SF-12, WHO-5, bespoke patient questionnaire (to be started during the ERT visit and finished at home), bespoke Fatigue Likert scale second and third completion (to be completed on the evening of the ERT administration visit and the next day), WPAI first completion (to be completed at home between 1 and 7 days after the ERT infusion [ideally in first 2 days]), WPAI second completion (to be completed on the day of the patient's next ERT administration visit). Caregiver questionnaires will be presented in the following order: CSI, bespoke caregiver questionnaire (to be started during the ERT administration visit and finished at home), WPAI:CG first completion (to be completed at home between 1 and 7 days after the ERT infusion), WPAI:CG second completion (to be completed on the day of the patient's next ERT administration visit).

The full schedule for completion of the study questionnaires for patients and caregivers is provided in Table 3 below.

Table 3. Timeline of completion and list of questionnaires administered to patients and caregivers

Participant group	Timeline of questionnaire completion			
	During ERT infusion visit	**Evening of ERT infusion**	**1-7 days after ERT infusion**	**Day of next ERT infusion (~15 days after previous infusion)**
Patients with FD	• Bespoke Fatigue Likert scale • SF-12 • WHO-5 • Bespoke patient questionnaire (to be started during ERT infusion visit and finished at home)	• Bespoke Fatigue Likert scale	<u>On Day 1 after ERT infusion:</u> • Bespoke Fatigue Likert scale <u>Any day 1-7 after ERT infusion:</u> • WPAI	• WPAI
Caregivers of patients with FD	• CSI • Bespoke caregiver questionnaire (to be started during ERT infusion visit and finished at home)	-	<u>Any day 1-7 after ERT infusion:</u> • WPAI:CG	• WPAI:CG

SF-12: Short Form-12 questions, WHO-5: World Health Organisation 5 questions, WPAI: Work Productivity and Activity Impairment, CG: Caregiver.

9.2 Setting

Patients with FD who are receiving ERT and their caregivers will be identified and recruited from approximately 8-12 specialist centres across four countries (Taiwan, Turkey, Brazil and Japan). The number of sites needed to achieve the required sample size may vary between the participating countries; this will be determined by the study management company (in consultation with Amicus Therapeutics), depending on the number and size of potentially

eligible study sites in each country. It is anticipated that 2-3 sites will be required in each country.

The participating centres will be specialist hospitals or treatment centres with experience of treating patients with FD with ERT (agalsidase alfa or agalsidase beta or both), interest in taking part in the study and likely availability of the required number of eligible patients/ERT episodes during the recruitment period.

In some of the participating countries, the preparation and administration of ERT takes place exclusively in the hospital setting; in these countries the study will be conducted solely within the hospitals (or infusion centres affiliated to the hospitals) from which the patients and caregivers are recruited. In other countries, ERT preparation and administration can take place in both hospitals and community healthcare centres (i.e. primary care treatment facilities). In these countries, patients who receive ERT in primary care (and their caregivers) will still be identified and recruited from their main (specialist) hospital, but the time and motion component of the study (observation of ERT preparation and administration) and distribution of patient- and caregiver- reported outcome measures and questionnaires will take place at their community healthcare centre (from which the relevant approvals to conduct the study will also be obtained). In some cases, patients may attend their community healthcare centre for the ERT infusion to be set up, and return home to start/deliver the infusion; these patients (and their caregivers) will still be included in the study, and the total HCP/patient and caregiver time recorded as for other episodes while the patient attends the community healthcare centre. Patients will capture the infusion time themselves by completing the bespoke questionnaire provided.

It is not routine practice in the countries of study for ERT preparation and administration to take place exclusively in the home setting, or for HCPs to attend the patient's home to assist with the infusion, although this may occur in exceptional circumstances (for example, if the patient themselves is a trained HCP). For this reason, patients who prepare and administer their ERT exclusively in the home setting will be excluded from the study, as resource use is likely to be atypical.

9.3 Study time periods

It is anticipated that the prospective recruitment / data collection period for this study will be approximately 4-5 months, starting from the date on which the relevant approvals to conduct the study are in place. Ideally, a maximum of two episodes of care per patient during the data collection period will be included for the time and motion evaluation (except in exceptional cases where it is determined that it is required to observe three episodes per patient due to a limited number of available patients/episodes for observation). Patients with FD and their caregivers will be asked to complete the study questionnaires once during the data collection period, when the patient attends the hospital or treatment centre for administration of ERT; the exception is the work productivity questionnaire, which will be completed on two occasions and the bespoke Fatigue Likert scale, which will be completed on three occasions (as described above). Separate patient consents will be obtained for the time and motion evaluation and cross-sectional questionnaire completion so patients will have the option to take part in only one or both parts of the study, according to their preference.

9.4 Study population

The source population for this study is adult patients with FD, recruited from four countries (Taiwan, Turkey, Brazil and Japan) who attend the participating hospitals, treatment centres or community healthcare facilities for administration of ERT (as part of their routine treatment) during the data collection period, and their caregivers. It is anticipated that approximately 60 episodes of care (30 with agalsidase alfa and 30 with agalsidase beta) per country, ideally up to a maximum of two episodes per patient (except in exceptional cases where it is determined that it is required to observe three episodes per patient due to a limited number of available patients/episodes for observation), will be included in the time and motion study, and approximately 30 sets of patient questionnaires and 5 sets of caregiver questionnaires per country (in total) will be completed.

Patients and caregivers fulfilling the following criteria will be eligible for inclusion in the study:

9.4.1 Selection criteria for patients

Patient inclusion criteria

- Patients aged 18 years old or over at time of consent.

- Patients with a documented diagnosis of FD.
- Patients who have received ≥4 doses of ERT (with agalsidase alfa or agalsidase beta) for the treatment of FD.
- Patients who present to the participating hospital(s) or treatment centre(s) for administration of a dose of ERT (as part of their routine treatment) during the data collection period.

Patients who meet any of the following criteria will be excluded:

- Patients aged <18 years at time of consent
- Patients who are unable or unwilling to give consent for study participation.
- Patients for whom ERT preparation and administration takes place exclusively in the home setting.
- *For the time and motion evaluation:* Patients whose ERT is administered by a HCP who does not consent to be observed.

9.4.2 Selection criteria for caregivers

Caregiver inclusion criteria:

- Aged 18 years of age or over at time of consent.
- Self-identifies as a caregiver of a patient with FD for whom written informed consent has been obtained for inclusion in the study.

Caregivers who meet any of the following criteria will be excluded:

- Caregiver (and/or the patient with FD whom they support or care for) is unable or unwilling to give consent for study participation.

9.4.3 Selection criteria for staff (for time and motion study)

Staff inclusion criteria (for time and motion study):

- Members of the whole care team responsible for preparing and administering agalsidase alfa and agalsidase beta to patients with FD.
- Staff who have given written consent to be observed during the preparation and provision of care.

9.5 Patient identification, sampling and recruitment

Adult patients with FD who are receiving treatment with ERT will be identified from local databases and pharmacy records by members of the whole care team at each centre and assessed for eligibility in line with the inclusion criteria. Patients will be approached by a member of their care team, given information about the study and invited to consent to participate. Patients may be approached in advance of their next scheduled attendance for ERT administration (by telephone and/or post) or in person, at a routine hospital visit. If patients do not wish to complete the study questionnaires they are still eligible for the time and motion study (and vice versa), provided that consent for the relevant component of the study has been obtained. For patients who are eligible to be observed more than once (for the time and motion study), initial consent for observation of up to three episodes of care will be obtained, and will be confirmed verbally by their HCP before the second and third episode of care. Each patient will only be asked to complete one set of questionnaires (with the exception of the work productivity questionnaire, which will be completed twice and the bespoke Fatigue Likert scale, which will be completed three times), even if they contribute more than one episode of care to the time and motion study.

Caregivers will only be invited to participate in the study if the patient whom they care for also consents to study participation. Caregivers will be approached for consent when they attend the hospital or treatment centre with the patient for their ERT administration visit.

Consecutive eligible patients (and their caregivers) presenting at the participating centres during the prospective recruitment period will be included in the study until the required sample size is reached. It is anticipated that patient and caregiver recruitment will take place over a 4-5 month period, starting from the date on which the relevant approvals needed to conduct the study are in place.

Prior to commencement of data collection, HCPs at the participating centres (and community healthcare facilities, where relevant) who are involved in the administration of ERT will be identified and asked to provide consent to be observed in their provision of care. Consent from HCPs will be confirmed by the observer verbally before each episode of care.

9.6 Variables

Study endpoints will be reported using descriptive statistics of distribution, central tendency and dispersion as appropriate for the data collected, as outlined in Section 0.

The study endpoints and dataset required to address the study objectives are summarised in Table 4 (please note that the response categories listed below are indicative only; the final list to be collected will be specified in the case report form (CRF)/electronic CRF (eCRF) and associated guidelines).

Table 4. Endpoints and dataset required to address the study objectives

Endpoint to address the primary objective	**Dataset required to address the primary objective**
Endpoint(s) and dataset required to address the primary objective: To quantify the total time spent by HCPs in the preparation and administration of a single dose of ERT (with agalsidase alfa and agalsidase beta) in patients with FD.	
Primary endpoint: Summary measures of the total time spent by HCPs in the preparation and administration of a single dose of ERT in patients with FD; stratified by country and by ERT product (agalsidase alfa or agalsidase beta). Secondary endpoints: • Summary measures of the time spent by HCPs on the following tasks associated with the preparation and administration of a single dose of ERT (with agalsidase alfa or agalsidase beta) in patients with FD: ○ Pre-administration patient consultation.	For each episode of care: • Name/s of observer • Patient and staff ID • Episode date • Episode setting (hospital / infusion centre / primary healthcare centre / primary healthcare centre (preparation and set-up) with home infusion) / other (specify) • ERT product administered: agalsidase alfa (Replagal®, Shire or biosimilar) or agalsidase beta (Fabrazyme®, Sanofi Genzyme or biosimilar) • ERT dose administered. • Pre-medications administered

○ Infusion (and pre-medication) preparation activities. ○ Administration of ERT (and pre-medications). ○ Monitoring of patient during and after administration. ○ Completion of clinical documentation. ○ Any other ERT-administration related activities. • Distribution of the roles of HCP (physician / nurse / nurse assistant or healthcare assistant / pharmacist / pharmacy assistant / other) involved in each task. • Summary measures of the ERT dose administered.	• **Activities associated with the preparation and administration of ERT:** • Pre-administration patient consultation: ○ Time patient arrived in clinic room. ○ Time patient left clinic room. ○ Start and end time of patient consultation with HCP for pre-treatment assessment. ○ Start and end time of prescription writing (if additional to consultation time with patient). ○ Start and end time of pre-administration clinical documentation (if additional to consultation time with patient). ○ Role of HCP(s) involved (physician / nurse / nurse assistant or healthcare assistant / other [specify]). • Infusion (and pre-medication) preparation activities: ○ Start and end time of infusion (and pre-medication) preparation activities (note: the following activities [as appropriate] will be included

	in the total time, but the time for each separate activity will not be recorded]: pre-dispensing prescription review, label generation, collation of items prior to assembly, assembly of item/drug reconstitution, labelling of containers, accuracy check, prescription delivery). o Role of HCP(s) involved (physician / nurse / nurse assistant or healthcare assistant / pharmacist / pharmacy assistant / other [specify]). • ERT (and pre-medication) administration: o Time patient arrived in clinic for ERT administration o Time patient left clinic following ERT administration o Start and end time of pre-medication administration. o Start and end time of ERT infusion. o Start and end time of HCP activity for administration of IV agalsidase alfa or agalsidase

	beta (including administration of pre-medications). o Start and end time of HCP activity for patient monitoring during agalsidase alfa or agalsidase beta infusion o Role of HCP(s) involved (physician / nurse / nurse assistant or healthcare assistant / pharmacist / pharmacy assistant / other [specify]). • Post-administration assessment and documentation: o Start and end time of HCP activity for post-treatment patient assessment / monitoring. o Start and end time of HCP activity for completion of clinical documentation. o Role of HCP(s) involved (physician / nurse / nurse assistant or healthcare assistant / pharmacist / pharmacy assistant / other [specify]). • Other ERT-administration related activities o Start and end time of HCP activity for any other ERT-

	administration related activities (specify). ○ Role of HCP(s) involved (physician / nurse / nurse assistant or healthcare assistant / pharmacist / pharmacy assistant / other [specify]).
Endpoints to address the secondary objectives	**Dataset required to address the secondary objectives**
Secondary objective 1: To quantify the total patient time, costs (i.e. out-of-pocket expenses) and work-related absence associated with attendances for the administration of a single dose of ERT (with agalsidase alfa or agalsidase beta) in patients with FD.	
• Summary measures of the total patient time associated with attendance for the administration of a single dose of ERT (with agalsidase alfa or agalsidase beta) in patients with FD. To include: • Time spent travelling to and from the hospital or treatment centre • Time spent collecting ERT from pharmacy (where relevant) • Time from arrival in hospital/treatment centre to departure • Time from arrival in hospital/treatment centre to start of ERT infusion • In addition, if the patient started/delivered their ERT infusion at home following set-up at a primary healthcare centre, the	Patient responses to the bespoke study questionnaire: • Patient ID • Date of episode • Patient employment status (employed full time / employed part time / unemployed / retired / student / home-maker) • Were they accompanied to the hospital or treatment centre (by a relative or caregiver) or did they attend alone (accompanied / alone) • Time left home/work to travel to hospital or treatment centre • Time arrived at hospital or treatment centre • Time of start of ERT infusion.

following will also be included in the total patient time: • Duration of ERT infusion and any home-based post-administration activities. • Time spent travelling to and from treatment centre after ERT infusion (only if patient returned to treatment centre after ERT infusion) • Time spent at treatment centre after ERT infusion. • Summary measures of the total cost to patients (i.e. out-of-pocket expenses) associated with attendance for the administration of a single dose of ERT (to include the costs of travel / parking / subsistence / other costs). • Distribution of patient employment status and whether the patient attended the ERT administration visit accompanied by a relative/caregiver or alone. • Proportion of patients with work absence due to attendance for this ERT episode and number of paid / unpaid hours absent.	• Time left hospital or treatment centre to travel back to home/work. • Time arrived back at home/work. Whether patient returned to work on the day of the infusion or the following day. If the patient started their ERT infusion at home following set-up at a primary healthcare centre, the following will also be collected: • Start and end time of ERT infusion • Start and end time of any post-administration activities. • Time left home/work to return to hospital or treatment centre (if relevant) • Time arrived back at hospital or treatment centre (if relevant) • Time left hospital or treatment centre to travel back to home/work • Time arrived back at home/work • Did patient take any time off work to attend this ERT episode? If yes, number of paid / unpaid hours absent from work. • Number of hours worked during ERT infusion (if relevant). • Costs (i.e. out-of-pocket expenses) incurred by the patient that were directly related to this ERT administration episode (to include

	costs of travel / parking / subsistence / any other costs).
Secondary objective 2: To quantify the total caregiver time costs (i.e. out-of-pocket expenses) and work-related absence associated with accompanying a patient with FD for the administration of a single dose of ERT (with agalsidase alfa or agalsidase beta).	
• Summary measures of the total caregiver time associated with accompanying a patient with FD for the administration of a single dose of ERT (with agalsidase alfa or agalsidase beta). To include: • Time spent travelling to and from the hospital or treatment centre • Time spent collecting ERT from pharmacy (where relevant) • Time from arrival in hospital/treatment centre to departure • Time from arrival in hospital/treatment centre to start of patient's ERT infusion • In addition, if the patient started/delivered their ERT infusion at home following set-up at a primary healthcare centre, the following will also be included in the total caregiver time (if the caregiver was involved in the activity): • Duration of ERT infusion and any home-based post-administration activities. • Time spent travelling to and from treatment centre after ERT infusion (only if patient returned to treatment centre after ERT infusion and was accompanied by a caregiver)	Caregiver responses to the bespoke study questionnaire: • Caregiver ID and patient ID • Date of episode • Caregiver sex (male / female) • Caregiver age category (<20 years / 20<30 years, 30<40 years, 40<50 years, 50<60 years, 60<70 years, 70<80 years, 80 years or over) • Does the caregiver also have FD? • Caregiver employment status (employed full time / employed part time / unemployed / self-employed / retired / student / home-maker) • Caregiver relationship to patient (parent / spouse or partner / son or daughter / other relative / friend or neighbour) • Type and frequency of care or support provided by the caregiver to the patient with FD • Time left home/work to travel to hospital or treatment centre • Time arrived at hospital or treatment centre • Time of start of ERT infusion

• Time spent at treatment centre after ERT infusion. • Summary measures of the total cost to caregivers (i.e. out-of-pocket expenses) associated with accompanying a patient with FD for the administration of a single dose of ERT (to include the costs of travel / parking / subsistence / other costs). • Distribution of caregiver age, sex, employment status, relationship to the patient with FD, type/frequency of support provided and proportion with FD. • Proportion of caregivers with work absence due to accompanying the patient for this ERT episode and number of paid / unpaid hours absent.	• Time left hospital or treatment centre to travel back to home/work • Time arrived back at home/work. If the patient started their ERT infusion at home following set-up at a primary healthcare centre, the following will also be collected (if the caregiver was involved in the activity): • Start and end time of ERT infusion • Start and end time of any post-administration activities. • Time left home/work to return to hospital or treatment centre (if relevant and if accompanied by caregiver) • Time arrived back at hospital or treatment centre (if relevant) • Time left hospital or treatment centre to travel back to home/work • Time arrived back at home/work • Did caregiver take any time off work to attend this ERT episode? If yes, number of paid / unpaid hours absent from work. • Number of hours worked during ERT infusion (if relevant). • Costs (i.e. out-of-pocket expenses) incurred by the caregiver that were directly related to accompanying the patient for this ERT administration

	episode (to include costs of travel / parking / subsistence / any other costs).
Secondary objective 3: To describe patient-reported HRQoL (measured by the SF-12), wellbeing (measured by the WHO-5), levels of fatigue (measured by the bespoke Fatigue Likert scale) and work productivity (measured by the WPAI) in patients with FD treated with ERT (with agalsidase alfa or agalsidase beta).	
Summary measures of patients': • HRQoL (SF-12 scores / responses). • General wellbeing (WHO-5 scores / responses). • Level of fatigue (bespoke Fatigue Likert scale). • Levels of work impairment (WPAI scores / responses). Questionnaire scores and/or item responses will be reported using summary statistics, as appropriate to the questionnaire and in accordance with the licensed scoring manual / instructions for use.	• Patient SF-12, WHO-5, Fatigue Likert scale and WPAI responses and dates of completion. For the bespoke Fatigue Likert scale, times (hours and minutes) of completion will also be recorded.
Secondary objective 4: To describe work productivity (measured by the WPAI:CG) and the strain of care provision (measured by the CSI) in caregivers of patients with FD treated with ERT.	
Summary measures of caregivers': • Levels of work impairment (WPAI:CG scores / responses). • Levels of strain of providing care for a patient with FD (CSI scores / responses).	• Caregiver WPAI:CG and CSI responses and date of completion.

Questionnaire scores and/or item responses will be reported using summary statistics, as appropriate to the questionnaire and in accordance with the licensed scoring manual / instructions for use.	
Patients' demographic and clinical characteristics (all patients)	
Summary measures of (at date of consent, unless specified): • Sex. • Age at onset of first symptoms, at FD diagnosis and at date of consent. • Duration of ERT treatment. • ERT treatment. • FD phenotype (organs involved). • FD mutation ((if known). • Severity of FD (to be determined using the specified baseline information]). • Any other relatives (with whom the patient lives) with FD. • Number and type (agalsidase alfa / agalsidase beta) of ERT infusions received in the year prior to date of enrolment.	• Sex (male / female). • Date of consent. • Age at consent. • Age at onset of first symptoms. • Date of FD diagnosis. • ERT start date. • ERT treatment under observation (agalsidase alfa / agalsidase beta). • Number of ERT infusions received in the year prior to date of enrolment, by type of treatment (algasidase alfa, algasidase beta). • FD phenotype (organ involvement/complications), to include any current or prior history of: hypohidrosis, neuropathic pain (and/or acroparasthesia and/or acute pain crises), cornea verticillata, angiokeratomas, hearing impairment (including deafness and/or tinnitus), cardiac events (including rhythm and/or conduction disturbances, hypertrophic cardiomyopathy or left ventricular mass index [LVMi] above normal range, myocardial infarction

	[MI], unstable angina, congestive heart failure, major cardiac medical procedures), renal events (including reduced estimated glomerular filtration rate [eGFR], abnormal albumin creatinine ratio [ACR], proteinuria or albuminuria, dialysis, kidney transplant), central nervous system (CNS) involvement (including brain magnetic resonance imaging [MRI] changes [white matter lesions], transient ischaemic attack [TIA] or stroke), FD-related gastrointestinal [GI] symptoms, plasma lyso-Gb3 levels above normal, low white blood cells (WBC) alpha-galactosidase, other: specify) • eGFR at enrolment (closest measurement prior and preferably within 12 months); date and measurement. • Urine protein levels at enrolment (closest measurement prior); date and measurement. • WBC alpha-galactosidase (closest prior to enrolment); date and measurement • LVMi at enrolment (closest measurement prior and preferably within 12 months); date and measurement.

	• FD mutation (name of mutation, if known, including: e.g. A143T)
	• Severity of FD (mild / moderate / severe), to be determined using the following baseline information:
	  ○ Type of FD (classical / non classical). If type is unavailable, it will be inferred from the information collected below*.
	  ▪ Number of organs involved (per medical history, as detailed above).
	  ▪ eGFR at enrolment.
	  ▪ Urine protein levels at enrolment.
	  ▪ LVMi at enrolment.
	  ▪ WBC alpha-galactosidase at enrolment.
	• Do any other relatives with whom the patient lives have FD (Yes / No / Not known).
	
	*FD will be defined as classical if (1) multi-organ disease at baseline (≥ 2 organs) as determined by medical history or baseline values for eGFR, urine protein, LVMi, AND (2) white blood cells alpha-

	galactosidase below cut-off at baseline (≤3% wild-type).

9.7 Data source

Patients' demographic and clinical data will be sourced from patients' medical records and other systems within the main (specialist) participating FD centres.

For the time and motion component of the study, prospective data relating to HCP time associated with the preparation and administration of a single dose of ERT will be captured by direct observation of HCPs during the episode of care by an independent external observer or a member of the patients' care team.

Patient- and caregiver-reported outcomes will be reported directly by patients and their caregivers using anonymised-coded paper-based questionnaires. Questionnaires will be given to consenting patients and caregivers by members of the patients' whole care team during an ERT administration visit. If the ERT infusion takes place in a hospital or treatment centre, it is anticipated that the validated questionnaires (with the exception of the first work productivity questionnaire) will be completed by the patient or caregiver during the ERT infusion and returned to centre staff in sealed envelopes for forwarding to the study management company, before they leave the clinic. The first work productivity questionnaire will be completed by the patient or caregiver at home between 1 and 7 days after date of the patient's ERT infusion. The bespoke questionnaire (which requires the patient or caregiver to document the time of leaving the clinic and the time to return to home/work) will also be completed by the patient or caregiver after leaving the clinic and returned to the centre (together with the first work productivity questionnaire) at a later date, either in person (at the patient's next ERT administration attendance) or by post (using a pre-paid envelope). Alternatively, their responses to the first work productivity questionnaire, the bespoke questionnaire and the bespoke Fatigue Likert scale may be collected over the telephone during call with a member of the patient's care team, or following a reminder call from a member of the patient's care team to fill in the questionnaires. If part of the episode of care takes place in the patient's home, it is likely that all study questionnaires will be completed by the patient or caregiver at home and returned to the centre as described above.

9.8 Study size

This study aims to recruit sufficient patients to record 30 episodes per treatment per country. Given this, the number of patients recruited will range from 15 to 30 per treatment per country. To evaluate the value of the sample estimates of the population that this sample size will allow for, it will be assumed pessimistically that each patient will have one measurement; the estimates once the study is carried out will therefore have higher precision than calculated below.

The anticipated length of time for pre and post-administration activities and infusion for each treatment utilised estimates from the research of Guest et al.[17] alongside clinical opinion sourced from sites in the countries of study; it was estimated that pre-administration processes would always take between 10-30 minutes, post-administration processes would take between 15-30 minutes, infusion of agalsidase alfa takes between 40 to 60 minutes and infusion of agalsidase beta would take between 90 to 180 minutes. To anticipate the precision of estimates given the sample size above, it was estimated that these times would follow a normal distribution within these ranges (as a result, the mean could be estimated by taking the middle value of the range and the standard deviation roughly approximated accordingly).

It is important to account for the fact that Fabry disease is rare and that the sample collected will represent a large proportion of the total population with disease. For instance, in the US, it was estimated that there were only approximately 7700 patients in total out of a population of about 323 million in 2016, which suggests that only 0.0024% have the disease. The estimated number of Fabry disease patients in other countries can be calculated from the prevalence of the disease in the US, by multiplying the expected proportion of the population with the disease (assuming that the prevalence is similar in the US to other countries) with the estimated total population (Brazil, Japan, Taiwan and Turkey therefore could have an estimated patient population of about 5015, 3033, 573 and 1934 patients respectively based on estimates of total population of 210 million, 127 million, 24 million and 81 million patients respectively[24]). Accounting for this, the estimated precision of estimates of time at different sample sizes for the largest and smallest countries in the study by population can be seen in the table below.

Table 5. Sample size estimations

Cohort	Activity / Estimate	95% confidence interval at different sample sizes			
		15 patients	**20 patients**	**25 patients**	**30 patients**
Brazil	Pre-Admin activity Mean: 20 minutes	17m 14 - 22m 46	17m 40 - 22m 20	17m 56 - 22m 04	18m 08 - 21m 52
	Post-Admin activity Mean: 22 mins 30	20m 26 – 24m 34	20m 45 – 24m 15	20m 57 – 24m 03	21m 06 – 23m 53
	ERT Alfa Mean: 50 minutes	47m 14 – 52m 46	47m 40 – 52m 20	47m 56 – 52m 04	48m 08 – 51m 52
	ERT Beta Mean: 135 minutes	122m 33 – 147m 27	124m 29 – 145m 31	125m 44 – 144m 16	126m 37 – 143m 23
	Overall Alfa Mean: 92 mins 30	84m 54 – 100m 06	86m 05 – 98m 55	86m 50 – 98m 10	87m 23 – 97m 37
	Overall Beta Mean: 177 mins 30	160m 13 – 194m 47	162m 54 – 192m 06	164m 38 – 190m 22	165m 52 – 189m 08
Taiwan	Pre-Admin activity	17m 16 – 22m 44	17m 42 - 22m 18	17m 59 - 22m 01	18m 08 - 21m 52

	Mean: 20 minutes				
	Post-Admin activity Mean: 22 mins 30	20m 27 – 24m 33	20m 46 – 24m 14	20m 59 – 24m 01	21m 06 – 23m 54
	ERT Alfa Mean: 50 minutes	47m 16 – 52m 44	47m 42 – 52m 18	47m 59 – 52m 01	48m 08 – 51m 52
	ERT Beta Mean: 135 minutes	122m 42 – 147m 18	124m 39 – 145m 21	125m 55 – 144m 05	126m 37 – 143m 23
	Overall Alfa Mean: 92 mins 30	84m 59 – 100m 01	86m 10 – 98m 50	86m 57 – 98m 03	87m 23 – 97m 37
	Overall Beta Mean: 177 mins 30	160m 24 – 194m 36	163m 07 – 191m 53	164m 52 – 190m 08	165m 52 – 189m 08

The higher the number of patients available to sample from the more precise the estimates of time taken for each activity will be, yet even at a worse-case scenario, 95% confidence intervals should be sufficient to describe the burden associated with ERT administration. Estimates taken from countries where the sample size represents a higher proportion of the total population with the disease, such as Taiwan will also be slightly more precise.

Therefore, the target sample size for the time and motion evaluation undertaken as part of this study is 240 ERT episodes, including 60 ERT episodes (30 for agalsidase alfa and 30 for

agalsidase beta) in each participating country. Ideally, a maximum of two ERT administration episodes will initially be observed per patient (except in exceptional cases where it is determined that it is required to observe three episodes per patient due to a limited number of available patients/episodes for observation), and at least 30 patients are expected to be enrolled in each country. For countries with limited FD patient numbers, a review of episodes of care observed will be completed on an ongoing basis. It may be determined that it is possible to observe three episodes per patient in these circumstances, however only two episodes will be observed per patient wherever possible.

For the questionnaire evaluation, approximately 120 patients and 20 caregivers will be expected to fill questionnaire sets (approximately 30 patients' and 5 caregivers' questionnaire sets per county).

9.9 Data management

9.9.1 Data collection

Patient demographic data will be collected using an anonymised-coded standardised eCRF designed specifically for the study. Patients will be identified in all study records by a unique study code to link multiple study records for each participant (if applicable) and preserve patient confidentiality. Data will be collected by members of the care team at each centre or external researchers (to be confirmed in each country prior to study commencement) using an electronic data capture (EDC) system through eCRFs.

For the prospective time and motion component of the study, trained external observers who are independent of the care process will attend the hospital or treatment centre and observe consenting patients' episodes of care. Alternatively, episodes of care may be observed by trained members of the patients' care team at each site, who are not performing the tasks that are being observed. Data will be collected about the procedures involved in the preparation and administration of ERT with agalsidase alfa or agalsidase beta, the job roles of HCPs involved and the time taken to complete the activities (start and stop time for each activity); this will be measured from the start of the first activity related to ERT preparation / administration (e.g. start of the pre-infusion clinical assessment) until completion of the last activity related to ERT preparation / administration (e.g. completion of the post-infusion documentation). The time taken to prepare and dispense the relevant medication will also be

collected by observation of pharmacy or nursing staff (as appropriate). Data for the time and motion component of the study will be collected using an anonymised-coded standardised paper-based CRF designed specifically for the study. The anonymised-coded data will then be transcribed into the eCRF by an appropriate member of staff.

Data management for eCRFs will be carried out using MACRO™, a data management system which has a secure web-based data entry interface and is fully validated and compliant with Food and Drug Administration (FDA) Information Governance standard 21 Code of Federal Regulations (CFR) Part 11. The MACRO™ system has restricted access, role-based permissions for data entry management and analysis and maintains an audit trail of all changes to data and activity in the system in line with 21 CFR Part 11. Members of the whole care team and external researchers will be trained in data entry into the eCRFs by study management staff from Open Health. Entry to MACRO™ will be restricted (by password protection) to only those members of staff directly involved with the study.

Consenting patients and caregivers will be given the relevant paper-based patient- and caregiver-reported outcome measures to complete either during the visit to the hospital or treatment centre for administration of ERT or at home after leaving the clinic (as described above). Completed questionnaires will be handed back or posted (using a pre-paid envelope) to the hospital or treatment centre staff or, alternatively, responses to the questionnaires completed by patients and caregivers after leaving the clinic (bespoke questionnaire, second and third bespoke fatigue Likert scale and first WPAI questionnaire) may be collected over the telephone during a call with a member of the patient's care team. The hospital or treatment centre staff will forward the completed questionnaires to the study management company for entry into a bespoke study database in Microsoft Excel™. Entry to the study database will be restricted (by password protection) to only those members of staff directly involved with the study.

Data will be prepared for analysis using R statistical software version 3.4.1, Stata™ (StataCorp LLC) version 14 and/or Microsoft Excel™. Data management and handling of data will be conducted according to the study-specific data management plan (DMP).

9.9.2 Data analysis

A detailed description of study analysis and reporting will be provided in a separate statistical analysis plan (SAP) to be finalised before data collection is completed. Analyses will be carried out by Open Health using R statistical software, Stata™ (StataCorp LLC) version 14 and Microsoft Excel™. Data will be analysed separately for each participating country and by ERT treatment (agalsidase alfa /agalsidase beta).

The planned statistical analyses are summarised below.

This study is designed to be descriptive in nature; there is no *a priori* hypothesis to be tested and therefore no comparisons between patient subgroups or treatments will be made. Distributions and descriptive statistics of central tendency (medians and arithmetic or geometric means) and dispersion (standard deviation [SD], interquartile range [IQR], range) will be presented for quantitative variables. Categorical variables will be described with frequencies and percentages; where appropriate, distributions, modes, medians, IQR and range will be reported. Where appropriate, 95% confidence intervals (95% CI) will also be presented for means and estimates of proportions. Ordinal variables will be evaluated using either frequencies and percentages or medians and IQR or both depending on the number of possible values for the variable.

Analysis for validated instruments will adhere to the licensed scoring manual. Item and domain scores (if relevant) will be presented.

All percentages will be reported to the nearest whole number; therefore, in reporting study results in tables, figures and associated text, percentages may not add up to 100% due to rounding. For total group/subgroup sizes of less than 10, percentages will not be reported, except under exceptional circumstances. Consideration will be given during data analysis as to whether reporting any of the planned analyses may identify individuals from combinations of variables occurring in very small groups; to preserve participant anonymity such results may be suppressed in the study report and any materials intended for publication.

9.9.3 Missing data

Where dates are ambiguous because of missing day and/or months, standard imputation will be applied: where day is missing the 15th of the month will be assumed; where both day and month are missing the 1st July will be assumed.

For other missing data, the affected analyses will be conducted using only the results of those patients/episodes with data available and the number included in each analysis will be stated.

The number of patients or caregivers with data missing will be reported for each study variable.

9.9.4 Subgroup and sensitivity analyses

The primary endpoint (and secondary endpoint, if numbers are sufficient) analyses will be conducted overall and repeated with stratification of the sample by country and by type of ERT (agalsidase alfa / agalsidase beta). If numbers are sufficient, analyses may be conducted by severity of FD (mild / moderate / severe [to be determined using the patients' baseline information, as described above]).

No sensitivity analyses are planned.

9.9.5 Interim analyses

No interim analyses are planned.

9.10 Quality control

All staff collecting data for the study (site staff and/or external observers) will be provided with data collection guidelines and will receive training in the requirements of the study protocol and correct data collection. This will ensure consistent completion of the eCRF for demographic information, paper CRF for time and motion data collection, and administration of paper questionnaires to patients and caregivers.

Data collection for the prospective time and motion study will be performed by trained external observers from the study management company or by members of the patients' care team at each site, who will also receive training in the time and motion study procedures. The observers will record start and stop times for each task on paper CRFs. It is recommended that 2 timing devices are used in case of failure of one of the devices. For the purposes of quality control, each data collector will transcribe the first 3 completed CRFs into the eCRF within 1 business day of the data collection and the entered data will be reviewed by project management or data management staff from the study management company. If errors or inconsistencies in the data are noted, additional training will be provided to the observers.

This pilot exercise will also be used to confirm that the database and CRF have been designed appropriately and that the data collection methodology is feasible.

Data collection progress will be monitored by local Clinical Research Associates (CRAs) on an ongoing basis and support will be available throughout the entire study period to observers and site study staff as required.

Patient demographic data and data submitted for the time and motion component of the study will be checked for completeness and accuracy by the Open Health data management team using agreed manual and programmed validation checks, which will be specified in the study DMP. Missing values may occur during collection of observational data (e.g. due to stopwatch failure). The frequency of these missing values will be tabulated as part of the data analysis but no queries will be raised. Other queries related to out-of-range values, inconsistent responses and any other data issues will be raised with each site by the data management team at the study management company, and resolutions documented. Study centres will be required to co-operate with the data management team in the resolution of these queries.

No queries will be raised on patient- or caregiver-reported data.

9.11 Limitations of the research methods

- Patient and caregiver consent is a requirement of this study; this may introduce selection bias and result in a study sample that may not be representative of the wider patient and caregiver population of interest.
- Centres will be selected on the basis of interest in taking part in the study and experience in treating patients with FD with ERT. It is acknowledged that these centres may not be representative of current wider clinical practice in the countries of study.
- For patient- and caregiver-reported outcomes, the data will rely on the completeness of the answers provided by participants, which will not be queried or otherwise followed up to clarify inconsistencies or omissions and may be subject to reporting bias.
- A limitation of asking patients to complete questionnaires during their ERT infusion is that they may feel more anxious and/or tired when they are attending the hospital to receive treatment than at other times; consequently, the descriptions of patient-

reported HRQoL and general wellbeing obtained in the study may be an overestimate of the overall impact of FD.

- This is a descriptive study and no analyses to control for confounding will be carried out. For ethical reasons, time and motion data will not be stratified by individual staff member, although the performance of staff may be a factor in any observed variability. Experience levels of staff performing tasks observed in the study may vary between centres and may not reflect the experience level of staff performing the same tasks outside the study centres. There are also likely to be differences between the participating countries in local clinical protocols, healthcare settings and care processes, which may introduce variability in the data collected.
- It is acknowledged that the time and motion evaluation may not capture the full burden of ERT administration since first infusions (which are expected to take longer than subsequent infusions) are excluded from the study; this is because the longer first infusion represents only a one-off burden at the start of long-term (potentially lifelong) treatment.
- It is also acknowledged that QoL data could be impacted by ERT episodes that are close in timing to each other.

10. Other aspects

10.1 Review of study results

Analysis of the primary endpoint, the total time spent by HCPs in the preparation and administration of a single dose of ERT in patients with FD, will be independently reviewed by a member of the Data Analysis team at Open Health who was not involved in the analysis of the final study data. No additional analysis checks will be carried out.

It is anticipated that study results will be presented to investigators to enable a preliminary discussion of the results of the study, at a meeting to be planned after completion of the data analysis and before the study report is prepared.

10.2 Study Amendments and Study Termination

Amendments to the study must be made only by prior agreement between the Amicus Therapeutics and Open Health. The Independent Ethics Committee (IEC)/Institutional Review Board (IRB) must be informed of all amendments and give approval for substantial amendments. The local Principal Investigator is responsible for obtaining approval from the IEC/IRB, and the local Clinical Research Organisation (CRO) supporting them will ensure a copy is forwarded to Amicus Therapeutics.

Open Health, Amicus Therapeutics and Principal Investigators reserve the right to terminate participation in the study according to the study contract. Open Health will notify the IEC/IRB in writing of the study's completion or early termination and send a copy of the notification to Amicus Therapeutics.

11. Protection of human subjects

This study will comply with all applicable laws, regulations, and guidance regarding patient protection including patient privacy, and consistent with the ethical principles of the Declaration of Helsinki[24], the requirements of the General Data Protection Regulation (GDPR)[25] and any other relevant local regulations. This study has been designed to minimise the data collected to that which is required for the planned analyses. The data collected will not include any direct identifiers. Data will be transferred to, and held securely by, Open Health at their offices within the UK during the conduct of this study, supported as needed by their local partners (refer to section 0).

11.1 Ethical and regulatory approvals

IEC/IRB approvals, competent authority and local management approvals for the conduct of this study and the sharing of anonymised-coded patient and caregiver data will be sought according to applicable local regulations.

11.2 Ethical considerations

This is an observational study involving a prospective time and motion study, completion of questionnaires by patients with FD and their caregivers and collection of demographic data from medical records; there will be no changes to patient management and no additional visits are required for the study. Only anonymised-coded data will be collected.

A participant information sheet will be provided to patients and caregivers identified as being eligible for study participation by the patient's whole care team, explaining the above components of this research study. Only patients providing written informed consent (for one or both components) will be included in the study and no data collection will take place until written informed consent for the relevant component of the study has been provided. Caregivers will only be included if the patient with FD for whom they provide care or support has also consented to join the study. HCPs at the participating centres will give consent to be observed in their provision of care for the time and motion study.

Patient- and carer-reported outcome data will be collected prospectively for those providing informed consent. Participation requires patients to complete a ~25-30 minute series of questionnaires related to the impact of FD on HRQoL, wellbeing, levels of fatigue and work productivity, which some may find upsetting. As most patients will complete the validated questionnaires during an ERT infusion, their HCPs will be able to provide support in the event that they do experience any distress. There will be no direct benefits of participation in the study but patients will be provided with a name and contact details for study-related queries.

Patients and caregivers will be able to withdraw from the study at any time without any impact on the patient's clinical care.

11.3 Participant privacy

The Data Controller for this study is Amicus Therapeutics. Data will be collected in anonymised-coded format and no personally identifiable information on any participant will be collected or removed from the hospitals or treatment centres participating in the study in order to preserve patient confidentiality. Participants will be assigned a study-specific unique identification number which will be referenced in a study log. This identification log will not leave the participating centre location and will be the responsibility of the principal investigator at that study centre. Anonymised-coded participant data will be processed for the purposes of the research study described in this protocol and will be shared with Amicus Therapeutics, Open Health, Klinikos, Zeincro and IQVIA within the European Economic Area (EEA) and, intellim Holdings Corporation and Clinical Trial & Consulting based outside the EEA for the purposes of this research study. Companies located outside the EEA will maintain anonymised-coded data in accordance with the recognised EU Model Clause Agreement to

safeguard participant anonymity. Participant data will be retained for the archive period specified in section 11.4. Participants will be advised of their rights in respect of their data, including the right to raise any concerns or complaints related to this research study with the applicable local data protection regulator.

11.4 Study Documentation and Archive

Consistent with ENCePP/ISPE/GDPR guidance, the study documents and anonymised-coded data will be archived securely by Open Health on behalf of Amicus Therapeutics for a period of three years in the UK after the end of the study (defined as the date of the final signed Study Report). After this time, the electronic patient-level study data will be removed of unique study codes (i.e. completely anonymised) and transferred securely to Amicus Therapeutics for extended archiving in line with their standard archive period for non-clinical trials. All other study documents will, with Amicus Therapeutics approval, be securely destroyed. The duration of archiving of study data will ensure that any queries arising from peer review of any ensuing publications can be addressed by reference to the source data if required.

12. Management and reporting of adverse events / adverse reactions

No patients will have received treatment with any Amicus Therapeutics medicinal products as part of this study, therefore it is not anticipated that Adverse Events (AEs), as defined below, will be required to be reported for study patients.

However, any AEs reported by an HCP in relation to patients that have received an Amicus Therapeutics product in the course of normal clinical practice will be reported in line with the guidance below. These events will be summarised in the safety reporting section of the final study report.

Sites will be advised that any untoward medical occurrence in a patient in this study following administration of a non-Amicus Therapeutics medicinal product should be reported as an AE to the authority marketing the product by the patient's HCP as per their local regulatory requirements.

12.1 Definitions

Adverse Event: Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

Adverse Drug Reaction (ADR):

As per the definition found in the WHO Technical Report 498 [1972], an adverse drug reaction is a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function

Product Complaints (PCs):

Product Quality Complaint (PQC) – Any communication that alleges deficiencies related to the drug product as a result of manufacturing, packaging, or distribution and calls into question the identity, strength, quality, potency, purity, tampering and/or counterfeiting of that marketed drug product . Product Quality Complaints (PQCs) can involve reports of product defects, such as product appearance, packaging issues, taste/odour etc. PQCs can also contain adverse events e.g., lack of efficacy (failing to produce the expected pharmacological action for the approved indication).

Non-Product Quality Complaint:

A complaint that does not directly relate to product quality, purity, strength, potency, safety or effectiveness, such as a service complaint.

Product Safety Events:

Post marketing Safety Events collectively refer to:

- All reports of AEs (non-serious and serious)
- AEs associated with product complaints, or counterfeit products
- Exposure during pregnancy and lactation (including paternal)
- Reports of overdose, misuse, abuse, drug interaction
- Medication error
- Off-label use with or without an AE
- Lack of efficacy
- Occupational exposure
- Suspected transmission of an infectious agent

Clinical trial safety events refer to:

Events specified to be collected and reported to Amicus pharmacovigilance (or designee) within the study protocol. This may include, but is not limited to serious adverse events, pregnancies, and overdose reports.

Serious Adverse Event:

A serious adverse event (experience) or reaction is any untoward occurrence that at any dose results in any of the following:

- Life-threatening AE: (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)
- Death
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Medically significant: (events that may not be life-threatening, result in death, or require hospitalization but may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject or may require medical or surgical intervention to prevent one of the outcomes listed in this definition above).

Special Situations (SS):

Circumstances where the report does not include an AE *per se*, but nevertheless needs to be reported to Amicus Therapeutics. These circumstances include as per GVP module VI (use in a paediatric or elderly population, overdose, off-label use, abuse, misuse, medication error, lack of therapeutic effect /lack of effect (LOE), occupational exposure, falsified medicinal product, suspected transmission of an infectious agent via a product, drug interactions (including drug/food, drug/device, and drug/alcohol interactions, drug/food interactions), unexpected therapeutic effect, or worsening of an existing condition

Unexpected Therapeutic Effect: a beneficial therapeutic effect of a Product aside from the use for which it had been given

12.2 Reporting Procedures for Adverse Events

12.2.1 Reporting Time-Frames

OPEN VIE shall report all potential AEs, SSs, and all PCs to Amicus within 24 hours of receipt of the event and no later than 1 business day. Reporting responsibilities are the same for all

AEs, irrespective of the seriousness of the event or whether or not it was caused by the product. All SSs, and PCs should be reported, whether or not there is an associated AE.

12.2.2 Reporting methodology

AEs, SSs, and PCs should be reported via email to PhV.Migalastat_SO@quintiles.com .

12.3 Reconciliation

At the end of the study (defined as after all study data is entered into the eCRF), IQVIA will email a report of cases received at IQVIA during the study to OPEN VIE. OPEN VIE is required to review the listing of cases and respond to IQVIA within 1 business day, confirming either that the list is correct or highlighting any discrepancies between the listing received from IQVIA and OPEN VIE records. Should OPEN VIE note that case reports are missing from the list provided by IQVIA, OPEN VIE will forward the missing report(s) within 1 business day via email to IQVIA at PhV.Migalastat_SO@quintiles.com. IQVIA will follow up any discrepancies to resolution.

13. Plans for disseminating and communicating study results

Study results will be submitted for presentation at appropriate national and/or international conferences and may also be submitted for publication to appropriate peer reviewed journals; the primary endpoint will be reported in the first publication arising from this study.

The study will be reported according to the requirements of STROBE (Strengthening the reporting of observational studies in epidemiology) as specified in the appropriate checklist for the study design[27].

Authorship of any publications arising from the study will follow the guidelines proposed by the International Committee of Medical Journal Editors (2015)[30]. All authors will meet the criteria for authorship, and all people who meet the criteria will be authors and all authors will agree to be accountable for the study. Potential conflicts of interest will be disclosed. All authors will have:

(1) made substantial contributions to conception or design or acquisition of data, or analysis and interpretation of data; AND

(2) participated in drafting the publication or revising it critically for important intellectual content; AND

(3) approved the final version to be published.

Each author will have participated sufficiently in the work to take public responsibility for appropriate portions of the content. Acquisition of funding, collection of data, or general supervision of the research group will not justify authorship.

14. Study support

The study is sponsored by Amicus Therapeutics. Amicus Therapeutics has commissioned Open Health to develop materials for and coordinate the conduct of the study, including protocol development, ethical and local approval, data collection, analysis and presentation of the results.

Open Health is an independent consultancy specialising in the evaluation of healthcare services and interventions through observational research, with a focus on the design and implementation of 'Real World Data' projects in order to understand current healthcare practices.

Open Health have commissioned local partner companies (Klinikos in Taiwan, Zeincro in Turkey, intellim Holdings Corporation in Japan and Clinical Trial & Consulting in Brazil) to perform local operations in these countries such as; site feasibility & identification, support of the sites to gain ethical and local hospital approval, data query management, site closure and local project management.

Amicus Therapeutics commission IQVIA as their pharmacovigilance vendor for collating and reporting all pharmacovigilance events related to Migalastat.

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16. Annex 1 Adverse event, special situation and product complaints intake form

EU/ROW Amicus Adverse Event/Special Situation and Product Complaints Intake Form

Email the completed form to: PhV.Migalastat_SO@Quintiles.com

1. Reporter's Information

☐ Health Care Professional (HCP) ☐ Consumer/ Patient ☐ Other _____

If Consumer Report, does the consumer give consent to contact their physician? ☐ Yes ☐ No If Yes, please provide Treating Doctor details below.

Reporters Contact Details:

First Name..... Family Name..... Occupation.....
Address..... City.....
ZIP/Post-Code..... Country..... State.....
Email..... Tel..... Fax.....
Signature..... Date..... *(DD/MM/YYY)*

Treating Doctor (if different from reporter)

First Name..... Family Name..... Specialty.....
Address..... City.....
ZIP/Post-Code..... Country..... State.....
Email..... Tel..... Fax.....

2. Patient Information

Initials:	Gender: ☐ Male ☐ Female ☐ Unknown	Date of Birth *(DD/MM/YYY)*: ..... Or Age: .....(Years)
Height: ..... ☐ cm ☐ m	Weight: ..... ☐ kg ☐ lbs	Ethnic Origin: .....
Pregnant:	☐ Yes ☐ No ☐ Not Applicable ☐ Unknown	

3. Suspect Product Details

Drug Name	Indication	Batch No/ Expiry date.	Start Date *(DD/MM/YYY)*	Stop Date *(DD/MM/YYY or state if ongoing)*	Unit Dose	Frequency	Route

Overdose: ☐ Yes ☐ No

Administration Error: ☐ Yes ☐ No If Yes please describe in Event Section below.

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Amicus Therapeutics

EU/ROW Amicus Adverse Event/Special Situation and Product Complaints Intake Form

Email the completed form to: PhV.Migalastat_SO@Quintiles.com

4. Event Details

Reported Event (list in order of importance)	Onset Date (DDMMMYYYY) Time to Onset	Resolved	Stop Date (DDMMMYYYY)	Relationship to Suspect Product	Serious
		☐ Yes ☐ No ☐ with sequelae		☐ Unrelated ☐ Unlikely ☐ Possibly ☐ Probably ☐ Related	☐ Yes ☐ No
		☐ Yes ☐ No ☐ with sequelae		☐ Unrelated ☐ Unlikely ☐ Possibly ☐ Probably ☐ Related	☐ Yes ☐ No
		☐ Yes ☐ No ☐ with sequelae		☐ Unrelated ☐ Unlikely ☐ Possibly ☐ Probably ☐ Related	☐ Yes ☐ No
		☐ Yes ☐ No ☐ with sequelae		☐ Unrelated ☐ Unlikely ☐ Possibly ☐ Probably ☐ Related	☐ Yes ☐ No

☐ **Hospitalized/ Hospitalization Prolonged**

Admission Date *(DDMMMYYYY)*:

........./........./.........

Discharge Date *(DDMMMYYYY)*:

........./........./.........

☐ **Death**

Date of Death *(DDMMMYYYY)*

........./........./.........

Cause: ....

Autopsy performed? ☐ **Yes** ☐ **No**

Autopsy report enclosed? ☐ Yes ☐ No

If reporter is HCP, tick all additional categories that apply:

☐ **Persistent or Significant Disability/ Incapacity**	☐ **Life Threatening**
☐ **Congenital Anomaly/ Birth Defect**	☐ **Medical / Surgical Intervention to prevent any of the above**

Was this event reported with a Product Complaint (PC)? ☐ **Yes** ☐ **No**

Is the complaint sample available? ☐ **Yes** ☐ **No**

If Yes, state PC Reference Number (if available): ....

Brief description of PC:

Additional Information (e.g. overall diagnosis, relevant investigations, previous episodes etc.):

Please provide a written summary of the course of the event, including signs, symptoms, severity, treatment and any other assessments which help to explain the event *(in case of insufficient space, please attach another blank page signed and dated)*.

5. Action Taken

☐ **Suspect Product Continued**

☐ **Suspect Product Dose Changed as a response to AE?**

Date of Change *(DD/MM/YYYY)*:...../...../.....

☐ **Suspect Product Withdrawn** **Date Withdrawn** *(DD/MM/YYYY)*: ...../...../.....

Symptoms Abated on Suspect Product Withdrawal ☐ **Yes** ☐ **No** ☐ **N/A**

☐ **Suspect Product Temporarily Withdrawn** **Date Withdrawn** *(DD/MM/YYYY)*: ...../...../.....

Date Restarted *(DD/MM/YYYY)*: ...../...../.....

Symptoms Abated on Product Withdrawal? ☐ **Yes** ☐ **No** ☐ **N/A**

Symptoms recurred on re-exposure to Suspect Product? ☐ **Yes** ☐ **No** ☐ **N/A**

☐ **Unknown**

Previous Exposure to Suspect Product? ☐ **Yes** ☐ **No** ☐ **N/A**

Similar Events After Previous Exposure? ☐ **Yes** ☐ **No** ☐ **N/A**

Treatment Given: ☐ **Yes** ☐ **No**

If Yes, state: .....

6. Relevant Medical History (including allergies, surgical procedures etc.that started PRIOR to use of Galafold)

Condition / Procedure	Start Date (DD/MM/YYYY)	Stop Date (DD/MM/YYYY or state (ongoing))	Comment

7. Concomitant Medications)

Concomitant Medication name	Start Date	Stop Date	Comment

17. Annex 2 Study questionnaires