

Retrospective and prospective observational study of MRI changes in bone and visceral lesions of patients with type 1 Gaucher disease treated with VPRIV® (velaglucerase alfa)

Study Title: Retrospective and prospective observational study of MRI changes in bone and visceral lesions of patients with type 1 Gaucher disease treated with VPRIV® (velaglucerase alfa)

Study Number: RMGF - SHPGCB-703

Study Phase: Retrospective and prospective observational study

Principal Investigator Nadia Belmatoug MD, Service de Médecine Interne - Centre de Référence des maladies lysosomales, Hôpital Beaujon, Clichy, France

Scientific Coordinators:

- David Petrover MD, hôpital Lariboisière, Clinique Bachaumont, Paris, France
- Luc Bracoud, Bioclinica, Lyon, France
- François-André Allaert, MD, PhD, CHRU Bocage, Dijon, France

Sponsor: Shire France

Sponsor Contact: Dr El Hadi Bessa
Email: ebessa0@shire.com

Original Protocol Version	15 th of September 2015
	Modified 05 april 2016

Confidentiality Statement

This document is the proprietary and confidential property of
Shire Rare diseases

SYNOPSIS

Sponsor : Shire France

Study Title: Retrospective and prospective observational study of MRI changes in bone and visceral lesions of patients with type 1 Gaucher disease treated with VPRIV® (velaglucerase alfa)

Study Number: RMGF - SHPGCB-703

Study Phase:

Non-Interventional, retro-prospective observational study

Rationale and background:

Gaucher's disease (GD) is a rare autosomal recessive disorder caused by the deficiency of the lysosomal glucocerebrosidase. This enzyme is required for the hydrolysis of glucosylceramide (or glucocerebroside) derived from degradation of the cell membrane of the formed elements of the blood. In GD, non-degraded glucosylceramide accumulates in lysosomes of the cells of the reticuloendothelial system and especially in macrophages.

The prevalence of MG is about 1/136 000 in the general population in France. Three main phenotypes (clinical forms) are traditionally distinguished:

- Type 1 accounts for 95% of cases. Its clinical expression is very heterogeneous ranging from asymptomatic throughout life to severe forms as soon childhood.
- Type 2 is an exceptional form (less than 1% of cases), with a very early expression (before the age of 1 year), and a very poor prognosis (death before the age of 2 years).
- Type 3 is a rare (less than 5% of cases) involving progressive encephalopathy of varying severity (oculomotor apraxia, epilepsy, ataxia) beginning before age 20 with similar forms than type 1 ⁽¹⁾.

The study will focus on the phenotype 1. The diagnosis of type 1 GD can be done at any age and its main manifestations are hepatosplenomegaly, thrombocytopenia, anemia, asthenia and occasionally incapacitating bone involvement (infarction, osteonecrosis, fractures, decreased bone density) causing acute and / or chronic pain. Bone involvement is the major complication of Gaucher disease whose manifestations are the leading cause of morbidity and disability ^(1, 2, 3).

Velaglucerase alfa in Gaucher's disease

VPRIV® is a long term enzyme replacement therapy in patients with Type 1 Gaucher disease.

The active substance of VPRIV, velaglucerase alfa is a glycoprotein made up of 497 amino acids and presents an amino acid sequence identical to the naturally occurring enzyme

glucocerebrosidase. There are five potential N-glycosylation sites, four of which are occupied. Velaglucerase alfa offsets or replaces beta-glucocerebrosidase (the natural enzyme responsible for the hydrolysis of glucocerebroside to glucose and ceramide in the lysosome) thus reducing the quantity of glucocerebrosides accumulated and correcting the physiopathology of Gaucher disease.

Justification of the study

Velaglucerase alfa increases the level of haemoglobin and the platelets count and reduces hepatic and splenic volumes in patients with type 1 Gaucher disease ⁽⁴⁾; promising results have also been observed in the domain of bone disorders ⁽⁵⁻¹⁰⁾. However, to date, the only MRI data available in French Gaucher patient's dossiers are qualitative data. This study with standardized reading MRIs, will provide for the first time objective and quantified data on organomegaly (liver and spleen volumes) as well as bone alteration (Bone Marrow Burden¹¹) of French patients treated with VPRIV®. These data will help to better assess the impact of this treatment on these parameters.

The result of this study will also answer in part to the request of the French Transparency Commission (CT: Commission de Transparence) of the French National Health Authority (HAS: Haute Autorité de Santé) to provide them with data of French patients treated with VPRIV®.

Objectives:

Primary Objective:

- To describe the changes of bone disease in femur and lumbar spine

Secondary Objectives:

- To describe the socio-demographic status of patients
- To describe the clinical evolution of patients (asthenia, abdominal pain, chronic bone pain, bone crises, hemorrhagic syndrome, hepatosplenomegaly, pulmonary, neurological)
- To describe the evolution of the parameters measured by MRI
 - Bone alterations (spine, pelvis, femurs, tibias and other symptomatic localization)
 - Visceral involvement (liver, spleen)
- To describe the evolution of biological parameters

If possible, to compare the evolution of MRI parameters between treatment-naïve patients and patients previously treated with another specific treatment for Gaucher disease at the baseline MRI.

Study Endpoints:

- **Primary Endpoint**

The primary endpoint is the change over time between the baseline MRI and the follow-up MRIs, of the BMB score weighted at T1 and T2 and measured at the femur and lumbar spine

- **Secondary and exploratory endpoints**

The secondary and exploratory endpoints of this study are:

- socio-demographic characteristics: age, sex, occupation
- history of the disease and context of diagnosis: age at diagnosis, type of symptoms, exams that allowed the diagnosis and its confirmation, enzymatic assay value genotype and presence or absence of family history
- medical history
- clinical evaluation criteria: weight (kg), height (cm), absence or presence (mild, moderate or severe) asthenia, abdominal pain, chronic bone pain, bone crises, bleeding syndrome, pulmonary impairment, neurological impairment
- clinical endpoints for liver and spleen
 - absence or presence of hepatomegaly, with the extent of the arrow (medio-clavicular line) (cm)
 - absence or presence of splenomegaly, with the extent of the costal overhang (cm).-
- liver evaluation criteria and spleen MRI
 - absence or presence of hepatomegaly, with the extent of the arrow (medio-clavicular line) (cm)
 - absence or presence of splenomegaly, with the extent of the costal overhang (cm)
 - liver volume (m³)
 - spleen volume (m³)
 - presence or absence of myocardial, nodules, fibrosis, vesicular stones or other alterations
- evaluation criteria of bone lesions by MRI (spine, pelvis, femurs, tibias and other symptomatic localization)

Absence or presence of bone lesions and their locations: bone infiltration, cortical thinning, osteonecrosis, bone infarction, stroke sequelae, vertebral compression, fracture or other bone disease
- evaluation criteria of the biological parameters:

hemoglobin (g/dl); leukocytes (cells/mm³); platelets (mm³); ACE (angiotensin converting enzyme (U/l); ferritin (mg/l); chitotriosidase (nmol/h/ml); CCL18 (ng/ml), vitamin D (nmol/L), vitamin B12 (pmol/l); SGOT/AST (U/l), SGPT/ ALT (U/l), GGT (U/l), alkaline phosphatase (U/l), triglycerides (mmol/l), total cholesterol (mmol/l) gamma globulin (g/l) serum calcium (mmol/l) presence or absence of a monoclonal peak and the type if any.

Study Population

To reflect the daily practices, this study includes all patients with a confirmed diagnosis of Type 1 Gaucher disease treated with VPRIV® at the date of beginning of the study and who meet the selection criteria of the study.

Study Inclusion and Exclusion Criteria

Inclusion Criteria

1. Patients of any age or gender with confirmed diagnosis of type 1 Gaucher disease,
2. Patients treated with VPRIV® at the beginning of the study. Prior starting VPRIV® patients could be either treatment naïve or previously treated with any other Gaucher treatment than VPRIV®
3. Patients should have one MRI data in the 5 previous years before starting VPRIV® Treatment (up to 3 months after initiation of VPRIV®)
4. Informed written consent obtained from the patient, and/or patient's parent(s), and/or legal representative. Assent, if old enough to grant, will be obtained from all patients under the age of 18 years

Exclusion Criteria

1. Patients for whom MRI is contra-indicated
2. Patients who did not had an MRI during the five years prior to the initiation of treatment with VPRIV® or within three months after initiation of VPRIV®.
3. Patients included in an ongoing clinical trial where the product is blinded

Study Design and duration

The study developed in conjunction with the French Referral Centers of Lysosomal Diseases and French Gaucher Treatment and Evaluation Committee (CETG: Comité d'Evaluation du Traitement de la Maladie de Gaucher) is a retro-prospective observational study of the French cohort of patients with type 1 Gaucher disease treated with VPRIV® in everyday clinical practice.

It consists of two phases: a retrospective and a prospective one with an inclusion period of 1 year.

Phase I: retrospective phase

The retrospective period includes the period between the date of the baseline MRI to the patient's date of inclusion in the study. The reference MRI is defined as the closest MRI to the initiation of VPRIV®, within the past five years, or within three months after initiation of VPRIV®.

Phase II: prospective phase

Prospective period will be one year from the date of patient inclusion in the study.

The final MRI

MRI being performed in current practice every 2 years, the final MRI follow-up performed corresponds to those in the previous year or in the year following the patient's inclusion.

The duration of the study will be 2 years, 1-year inclusion period to be sure to include all patients VPRIV® (reviewed annually in consultation each year) and a prospective follow-up period of 1 year.

Provisional timetable for the study:

CCTIRS / CNIL authorisation	October 23, 2015
Inclusion of the first patient in the study	September 30, 2016
Inclusion of the last patient in the study	September 30, 2017
Last visit of the last patient	September 30, 2018
Study clinical report	January 31, 2019

Data collection and transmission

All data entered will be used for analysis purposes and results will be submitted to inform regulatory agencies. Patient care and management is freely determined by the participating physician, in the framework of an observational study reflecting the daily medical practice. The clinical data, the results of routine clinical and laboratory testing that are part of standard medical care for patients with Gaucher disease will be collected from the medical record of the patient :

- Socio-demographic characteristics
- History of the disease and context of diagnosis
- Medical background
- MRI: abdominal and bone, as defined below
- Clinical data available in the range from 3 months before or after each MRI
- Biological data available in the range from 3 months before or after each MRI
- Treatment with VPRIV® (velaglucerase alfa), including the doses and regimens.

The MRI images collected during the study:

The MRIs performed in the patient's usual medical follow-up for its Gaucher disease (abdominal MRI (liver and spleen) and bone MRI (back injury pelvis, lower limbs) and / or whole-body MRI) will be collected. Among the MRIs available in the patient's medical records, MRIs will be collected as following:

- Reference MRI: MRI closest to the date of initiation of VPRIV® in the five years preceding the start of treatment or within three months after initiation of VPRIV®.
- MRIs of the retrospective phase of the study: All MRIs available between the reference MRI and the inclusion date of the patient.
- MRIs of the prospective phase of the study: all the MRIs that will be realized during the prospective phase of the study, that is to say during the year following the date patient inclusion in the study

Second reading of the MRI

The collected MRIs will be subject to a second reading, which will be conducted centrally by a medical image processing center (BioClinica).

This second reading of MRIs will particularly provide quantitative data not available initially in the patient records, such as BMB score at the lumbar spine and femur, and liver and spleen volumes.

In case the second reading provides additional data to the first reading, as any new comments or discordant diagnosis, the investigating doctor will integrate these data as soon as he has knowledge of them in the medical care of the patient.

MRI collection and transmission

Except the data from the second reading of MRIs by BioClinica, all data defined above, will be collected in the case report of the study, from the patient's medical record.

For the second centralized reading of the MRIs, the MRIs will be transmitted as follows: the investigation center will make a copy on CD-ROM of each MRI collected for the study needs, and will replace the identity the patient by an identification number whose correspondence with the patient's identity is only known by the investigation center. This patient identification number will be predefined and attributed to the patient's MRI when the patient is included in the study.

Copies of MRIs and coded will be sent securely at BioClinica center for analysis. In case of connection failure from the participating centers, MRI scans will be sent by post.

Data from this second reading by BioClinica will be retrieved for analysis. The results of the second reading by BioClinica will be forwarded to investigation center, which will include them in the patient's record.

Statistical analysis

Primary endpoint:

The values observed at the different follow up times and the variations between the reference MRI and the follow-up MRI, of the BMB weighted score at T1 and T2 measured at the femur and lumbar spine, are described by mean and standard deviation and the 95% confidence interval will be calculated. These values will be compared at the different follow up times by test on repeated data: ANOVA on repeated series or Wilcoxon rank test, depending on the nature and distributions of the studied variables.

Secondary endpoints:

Socio-demographic characteristics of the patients, history of their disease, context of diagnosis, medical history, clinical evaluation criteria of liver and spleen, MRI evaluation criteria of the liver and spleen, MRI evaluation criteria of bone lesions and the biological evaluation criteria are described by mean and standard deviation for quantitative variables, by frequency and percentage for categorical and ordinal variables. The 95% confidence intervals will be calculated. The evolutions of these criteria at the different periods when they are collected will be described by mean and standard deviation or percentage changes. They will be compared between the different times of the study by test on repeated data: ANOVA on repeated series or Wilcoxon rank test, depending on the nature and distributions of the studied variables.

Software

Data will be entered on CLINSIGHT and analysed with SAS 9.3.

Indirectly personal character of data

The patient information is sent to the radiological analysis centre in an indirectly personal form comparable to that used in therapeutic trials, namely the patient's initials and a file number. Only the practitioner at the Gaucher Disease Reference Centre knows the correspondence between this number attributed to the patient and the patient's identity.

Justification of indirectly personal character

This indirectly personal character (initials and file number which only the practitioner can match with the patient's identity) allows the practitioner to record successive follow-ups of the patient without any risk of mistaking files.

Patients' rights protection

It is the responsibility of the Investigator to obtain written Informed Consent and assent, where applicable from study patients. All consent and assent documentation must be in accordance with applicable regulations and GCP. Each patient or the patient's legally authorised representative as applicable is requested to sign the Patient Informed Consent. Form or a certified translation, if applicable after the patient has received and read (or been read) the written patient information and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences and the patient's rights and responsibilities. A copy of the informed consent and assent documentation (i.e., a complete set of patient information sheets and fully executed signature pages) must be given to the patient or the patient's legally authorised representative. If applicable, it is provided in a certified translation of the local language. Signed consent forms must remain in each patient's study file and must be available for verification at any time. Patients shall also be informed that they may decline to participate in the study without that being detrimental to the quality of care dispensed to them by their practitioner and that they have a right of access to this information through their Gaucher Referent Center.

Figure 1. Study flowchart

	0. Eligible patients (n= 40-50)	
	1. Patient inclusion (Written Informed Consent obtained)	
Retrospective data collection	<p>2. Retrospective data collection</p> <p><i>The closest MRI conducted during the 5 years before the initiation of VPRIV® treatment or in the 3 months after the Vpriv initiation is collected and corresponds to the reference MRI.</i></p> <p><i>Clinical and biological data available 3 months before or after the reference MRI are collected</i></p> <p><i>Medical history and clinical and biological data available, when VPRIV® treatment is initiated , are collected</i></p> <p><i>Each MRI available since Vpriv treatment initiation and patients inclusion is collected as well as clinical and biological data available 3 months before or after it</i></p> <p>.....</p> <p><i>MRI collected are anonymously sent to a central lab reading: MRI results data collection</i></p>	<p>Medical history</p> <p>Clinical data</p> <p>Laboratory data</p> <p>VPRIV® treatment</p> <p>MRI</p> <p>..... VPRIV treatment</p> <p>Centralized MRI reading:</p> <ul style="list-style-type: none"> - Liver and spleen volumes - BMB score of the spine and femur
Prospective data collection	<p>3. Prospective follow-up:</p> <p><i>For each MRI that will be conducted from the patient inclusion until the end of the one year follow up study, clinical and laboratory data available within the 3 months before the MRI and the 3 months after MRI are collected.</i></p> <p>.....</p> <p>.....</p> <p><i>MRI collected are anonymously sent to a central lab reading: MRI results data collection</i></p>	<p>Clinical data</p> <p>Laboratory data</p> <p>VPRIV® treatment</p> <p>MRI</p> <p>.....</p> <p>Centralized MRI reading:</p> <ul style="list-style-type: none"> - Liver and spleen volumes - BMB score of the spine and femur

TABLE OF CONTENTS

SYNOPSIS.....	2
TABLE OF CONTENTS.....	10
LIST OF APPENDICES.....	12
1 INTRODUCTION	13
1.1 Gaucher disease	13
1.2 Velaglucerase alfa in type 1 Gaucher disease.....	13
1.3 Justification of the study	13
2 STUDY OBJECTIVES.....	15
2.1 Primary Objective(s).....	15
2.2 Secondary Objective(s).....	15
3 STUDY ENDPOINT	16
3.1 Primary Endpoint(s).....	16
3.2 Secondary Endpoint(s).....	16
4 STUDY PLAN.....	17
4.1 Data collection and transmission	17
4.2 The MRI images collected during the study:.....	17
4.3 Second lecture of the MRI.....	17
4.4 MRI collection and transmission	18
4.5 Data collection and transmission	18
4.6 Indirectly personal character of data.....	19
4.7 Justification of indirectly personal character	19
4.8 Patients' rights protection	19
4.9 Overall Study Design and Plan	20
4.10 Rationale for Study Design.....	21
4.11 Rationale for centralized MRI measurements.....	21
4.12 Study Duration	21
5 STUDY POPULATION	22
5.1 Inclusion Criteria	22
5.2 Exclusion Criteria	22
5.3 Withdrawal of Patients from the Study.....	22
6 STUDY PROCEDURES	23
6.1 Informed Consent.....	23
6.2 Institutional Review Board or Independent Ethics Committee	23
6.3 Study Entrance Criteria.....	24
6.4 Confirmation of Study Eligibility	24
6.5 Demographics	24
6.6 Medical History	24

6.7	Efficacy and Effectiveness Assessments	26
6.8	Safety Assessments	29
6.9	Concomitant Medications, Therapies, and Medical/Surgical Interventions Assessments	29
6.10	Adverse Events Assessments	29
6.11	Serious Adverse Drug Reactions	32
6.12	Removal of Patients from the Study	34
7	QUALITY CONTROL AND ASSURANCE	36
7.1	Appropriateness of Measurements	36
7.2	Monitoring	36
8	PLANNED STATISTICAL METHODS	37
8.1	General Considerations	37
8.2	Determination of Sample Size	37
8.3	Analysis Populations	37
8.4	Demographics and Baseline Characteristics	37
8.5	Primary Endpoint(s) or Assessments	37
	Primary Safety Endpoint(s)	37
	Primary Efficacy/Effectiveness Endpoint(s)	37
8.6	Secondary Endpoint(s)	38
8.7	Interim Analysis	38
9	ADMINISTRATIVE CONSIDERATIONS	39
9.1	Investigators and Study Administrative Structure	39
9.2	Institutional Review Board or Independent Ethics Committee Approval and Other Governing Regulatory Bodies	39
9.3	Study Monitoring	39
9.4	Case Report Forms and Study Records	39
9.5	Critical Documents	40
9.6	Data Monitoring Committee and/or Adjudication Committee	40
9.7	Protocol Violations/Deviations	40
9.8	Premature Closure of the Study	41
9.9	Access to Source Documentation	41
9.10	Data Generation and Analysis	41
9.11	Retention of Data	41
10	REFERENCE LIST	42

LIST OF APPENDICES

Appendix 1	Protocol Amendment Summary of Changes.....	43
Appendix 2	Overview of the Study Design.....	44
Appendix 3	Protocol Signature Page.....	45

Abbreviations	Definition
AE	Adverse Event
CHMP	Committee for Medicinal Products for Human Use
CNS	Central Nervous System
CRO	Contract Research Organization
CSF	Cerebrospinal Fluid
CSR	Clinical Study Report
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EMA	European Medicines Agency
EOS	End Of Study
EW	Every Other Week
ERT	Enzyme Replacement Therapy
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma Glutamyl Transferase
GPP	Good Pharmacoepidemiological Practices
GVP	Good Pharmacovigilance Practice Guidelines
Hb	Hemoglobin
Hct	Hematocrit
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IRB	Institutional Review Board
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
SOE	Schedule Of Events
WHO-DD	World Health Organization Drug Dictionary

1 INTRODUCTION

1.1 Gaucher disease

Gaucher disease (GD) is a rare autosomal recessive disorder caused by the deficiency of the lysosomal glucocerebrosidase. This enzyme is required for the hydrolysis of glucosylceramide (or glucocerebroside) derived from degradation of the cell membrane of the formed elements of the blood. In GD, non-degraded glucosylceramide accumulates in lysosomes of the cells of the reticuloendothelial system and especially in macrophages.

The prevalence of MG in France is about 1/136 000 in the general population. Three main phenotypes (clinical forms) are traditionally distinguished:

- Type 1 accounts for 95% of cases. Its clinical expression is very heterogeneous ranging from asymptomatic throughout life to severe forms as soon childhood.
 - Type 2 is an exceptional form (less than 1% of cases), with a very early expression (before the age of 1 year), and a very poor prognosis (death before the age of 2 years).
 - Type 3 is a rare (less than 5% of cases) involving progressive encephalopathy of varying severity (oculomotor apraxia, epilepsy, ataxia) beginning before age 20 with similar forms than type 1 (1).
- The study will focus on the type phenotype 1. The diagnosis of type 1 GD can be done at any age and its main manifestations are hepatosplenomegaly, thrombocytopenia, anemia, asthenia and occasionally incapacitating bone involvement (infarction, osteonecrosis, fractures, decreased bone density) causing acute and / or chronic pain. Bone involvement is the major complication of Gaucher disease whose manifestations are the leading cause of morbidity and disability (1,2,3).

1.2 Velaglucerase alfa in type 1 Gaucher disease

VPRIV® is a long term enzyme replacement therapy in patients with Type 1 Gaucher disease. The active substance of VPRIV, velaglucérase alfa is a glycoprotein made up of 497 amino acids and presents an amino acid sequence identical to the naturally occurring enzyme glucocerebrosidase. There are five potential N-glycosylation sites, four of which are occupied. Velaglucerase alfa offsets or replaces beta-glucocerebrosidase (the enzyme responsible for the hydrolysis of glucocerebroside to glucose and ceramide in the lysosome) thus reducing the quantity of glucocerebrosides accumulated and correcting the physiopathology of Gaucher's disease.

1.3 Justification of the study

Velaglucerase alfa increases the level of haemoglobin and the platelet count and reduces hepatic and splenic volumes in patients with type 1 Gaucher disease (4), promising results have also been observed in the domain of bone disorders (5-10). However, to date, the only MRI data available in French Gaucher patients's dossiers are qualitative data. This study with standardized reading MRIs, will provide for the first time objective and quantified data on organomegaly (liver and spleen volumes) as well as bone alteration (score BMB) of French patients treated with VPRIV®. These data will help to better assess the impact of the treatment on these parameters. The result of this study will also answer in part to the request of the French Transparency Commission (CT:

Retrospective and prospective observational study of MRI changes in bone and visceral lesions of patients with type 1 Gaucher disease treated with VPRIV® (velaglucerase alfa)

Commission de Transparence) of the French National Health Authority (HAS: Haute Autorité de Santé) to provide them with data of French patients treated with Vpriv®.

2 STUDY OBJECTIVES

2.1 Primary Objective(s)

To describe changes in bone disease in femur and lumbar spine in Gaucher's disease patients treated with Velaglucerase alfa measured by MRI.

2.2 Secondary Objective(s)

- To describe the socio-demographic of patients;
- To describe the clinical evolution of patients (asthenia, abdominal pain, chronic bone pain, bone crises, hemorrhagic syndrome, hepatosplenomegaly, pulmonary, neurological,)
- To describe the evolution of the parameters measured by MRI
 - Bone alterations (spine, pelvis, femurs, tibias and other symptomatic localization)
 - Visceral involvement (liver, spleen)
- To describe the evolution of biological parameters

If possible, compare the evolution of MRI parameters between treatment-naïve patients and patients previously treated with another specific treatment for Gaucher disease at the baseline MRI.

3 STUDY ENDPOINT

3.1 Primary Endpoint(s)

The primary endpoint is the change over time between the baseline MRI and the follow-up MRIs, of the BMB score (11) weighted at T1 and T2 and measured at the femur and lumbar spine .

3.2 Secondary Endpoint(s)

The secondary and exploratory endpoint(s) of this study are:

- socio-demographic characteristics: age, sex, occupation
- history of the disease and context of diagnosis: age at diagnosis, type of symptoms, exams that allowed the diagnosis and its confirmation, enzymatic assay value, genotype and presence or absence of family history
- medical history
- clinical evaluation criteria: weight (kg), height (cm), absence or presence (mild, moderate or severe) asthenia, abdominal pain, chronic bone pain, bone crises, syndrome bleeding, pulmonary impairment, neurological impairment
- clinical endpoints of liver and spleen:
 - Absence or presence of hepatomegaly, with the extent of the arrow (medio-clavicular line) (cm)
 - Absence or presence of splenomegaly, with the extent of the costal overhang (cm).-
- liver evaluation criteria and spleen MRI:
 - Absence or presence of hepatomegaly, with the extent of the arrow (medio-clavicular line) (cm)
 - Absence or presence of splenomegaly, with the extent of the costal overhang (cm)
 - Liver volume (m3)
 - Spleen volume (m3)
 - Presence or absence of myocardial, nodules, fibrosis, vesicular stones or other alterations.
- evaluation criteria of bone lesions by MRI (spine, pelvis, femurs, tibias and other symptomatic localization)

Absence or presence of bone lesions and their locations: bone infiltration, cortical thinning, osteonecrosis, bone infarction, stroke sequelae, vertebral compression fracture or other bone disease
- evaluation criteria of the biological parameters: hemoglobin (g/dl); leukocytes (cells/mm3); platelets (mm3); ACE (angiotensin converting enzyme (U/l); ferritin (mg/l); chitotriosidase (nmol/ h/ ml); CCL18 (ng/ml), vitamin D (nmol/L), vitamin B12 (pmol / l); SGOT / AST (U/l), SGPT / ALT (U/l), GGT (U/l), alkaline phosphatase (U/l), triglycerides (mmol/l), total cholesterol (mmol/l) gamma globulin (g/l) serum calcium (mmol/l) presence or absence of a monoclonal peak and the type if any

4 STUDY PLAN

4.1 Data collection and transmission

All data entered will be used for analysis purposes and results will be submitted to inform regulatory agencies. Patient care and management is freely determined by the participating physician, in the framework of an observational study reflecting the daily medical practice. The clinical data, the results of routine clinical and laboratory testing that are part of standard medical care for patients with Gaucher disease will be collected from the medical record of the patient :

- Socio-demographic characteristics
- History of the disease and context of diagnosis
- Medical background
- MRI: abdominal and bone, as defined below
- Clinical data available in the range from 3 months before or after each MRI
- Biological data available in the range from 3 months before or after each MRI
- Treatment with VPRIV® (velaglucerase alfa), including the doses and regimens

4.2 The MRI images collected during the study:

The MRIs performed in the patient's usual medical follow-up for its Gaucher disease (abdominal MRI (liver and spleen) and bone MRI (back injury pelvis, lower limbs) and / or whole-body MRI) will be collected. Among the MRIs available in the patient's medical records, MRIs will be collected the following:

- Reference MRI: MRI closest to the date of initiation of VPRIV® in the five years preceding the start of treatment or within three months after initiation of VPRIV®.
- MRIs of the retrospective phase of the study: All MRIs available between the reference MRI and the inclusion date of the patient.
- MRIs of the prospective phase of the study: all the MRIs that will be realized during the prospective phase of the study, that is to say, during the year following the date patient inclusion in the study.

4.3 Second lecture of the MRI

The collected MRIs will be subject to a second reading, which will be conducted centrally by a medical image processing center (BioClinica).

This second reading of MRIs will particularly provide quantitative data not available initially in the patient records, such as BMB score at the lumbar spine and femur, and liver and spleen volumes.

In case the second reading provides additional data to the first reading, as any new comments or discordant diagnosis, the investigating doctor will integrate these data as soon as it has knowledge of them in the medical care of the patient.

4.4 MRI collection and transmission

Except the data from the second reading of MRIs by BioClinica, all data defined above, will be collected in the case report of the study, from the patient's medical record.

For the second centralized reading of the MRIs, the MRIs will be transmitted as follows: the investigation center will make a copy on CD-ROM of each MRI collected for the study needs, and will replace the identity the patient by an identification number whose correspondence with the patient's identity is only known by the investigation center. This patient identification number will be predefined and attributed to the patient's MRI the patient is included in the study.

Copies of MRIs and coded will be sent securely at BioClinica center for analysis. In case of connection failure from the participating centers, MRI scans will be sent by post.

Data from this second reading by BioClinica will be retrieved for analysis. The results of the second reading by BioClinica will be forwarded to investigation center, which includes them the patient's record.

4.5 Data collection and transmission

As part of their routine practice, the practitioners working at the Gaucher Referent Centers in France collect a basic information form regarding the management of their Gaucher patients as well as the MRI data of these patients followed in these referent centers.

For the needs of the study, the Gaucher Referent Centers make a copy of the MRI Cd-Roms and and replace the person's identity on the copy by a code for which the Reference Centre alone has the chart for cross-referencing with the patient's identity. This code is made up of the first two letters of the surname and the first letter of the first name and a file number.

The imaging data thus made anonymous with respect to third parties are then transmitted to French Gaucher Treatment and Evaluation Committee "CETG" which in turn transfer them to BIOCLINICA, the radiological analysis centre. The latter is in charge of conducting standardised measurements of the volume of their hepatosplenomegaly as well as the characteristics of their bone disorders.

The resulting data are then sent to the CETG which in turn transfer these data to the Referent Gaucher Centers (practitioner) which includes them in the patient's monitoring file.

4.6 Indirectly personal character of data

The patient information is sent to the radiological analysis centre in an indirectly personal form comparable to that used in therapeutic trials, namely the patient's initials and a file number. Only the practitioner at the Gaucher Disease Reference Centre knows the correspondence between this number attributed to the patient and the patient's identity.

4.7 Justification of indirectly personal character

This indirectly personal character (initials and file number which only the practitioner can match with the patient's identity) allows the practitioner to record successive follow-ups of the patient without any risk of mistaking files.

4.8 Patients' rights protection

It is the responsibility of the Investigator to obtain written Informed Consent and assent, where applicable from study patients. All consent and assent documentation must be in accordance with applicable regulations and GCP. Each patient or the patient's legally authorised representative as applicable is requested to sign the Patient Informed Consent.

Form or a certified translation, if applicable after the patient has received and read (or been read) the written patient information and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences and the patient's rights and responsibilities. A copy of the informed consent and assent documentation (i.e., a complete set of patient information sheets and fully executed signature pages) must be given to the patient or the patient's legally authorised representative. If applicable, it is provided in a certified translation of the local language. Signed consent forms must remain in each patient's study file and must be available for verification at any time.

4.9 Overall Study Design and Plan

Figure 1. Overview of the Study Design

	0. Eligible patients (n= 40-50)	
	1. Patient inclusion (Written informed consent obtained)	
Retrospective data collection	<p>2. Retrospective data collection</p> <p><i>The closest MRI conducted during the 5 years before the initiation of VPRIV® treatment or in the 3 months after the VPRIV® initiation is collected and corresponds to the reference MRI.</i></p> <p><i>Clinical and biological data available 3 months before or after the reference MRI are collected</i></p> <p><i>Medical history and clinical and biological data available, when VPRIV® treatment is initiated, are collected</i></p> <p><i>Each MRI available since VPRIV® treatment initiation and patients inclusion is collected as well as clinical and biological data available 3 months before or after it</i></p> <p>.....</p> <p><i>MRI collected are anonymously sent to a central lab reading: MRI results data collection</i></p>	<p>Medical history</p> <p>Clinical data</p> <p>Laboratory data</p> <p>VPRIV® treatment</p> <p>MRI</p> <p>..... VPRIV treatment</p> <p>Centralized MRI reading:</p> <p>- Liver and spleen volumes</p> <p>- BMB score of the spine and femur</p>
Prospective data collection	<p>3. Prospective follow-up:</p> <p><i>For each MRI that will be conducted from the patient inclusion until the end of the one year follow up study, clinical and laboratory data available within the 3 months before the MRI and the 3 months after MRI are collected.</i></p> <p>.....</p> <p>.....</p> <p><i>MRI collected are anonymously sent to a central lab reading: MRI results data collection</i></p>	<p>Clinical data</p> <p>Laboratory data</p> <p>VPRIV® treatment</p> <p>MRI</p> <p>.....</p> <p>Centralized MRI reading:</p> <p>- Liver and spleen volumes</p> <p>- BMB score of the spine and femur</p>
<p>The study will last for one year from the date of the patient inclusion</p> <p>The study is constituted of 2 phases: a retrospective and a prospective period</p> <p><u>Phase I: Retrospective period</u></p> <p>The retrospective period includes the period before VPRIV® treatment initiation until the beginning of this study..</p> <p><u>Phase II: Prospective period</u></p> <p>The prospective period will last for one year from the date of the patients inclusion</p>		

4.10 Rationale for Study Design

Retrospective-observational studies are required to describe population treated in the daily practice, the use of the drug and its effect and safety in real life conditions.

4.11 Rationale for centralized MRI measurements

It is customary for any multi-center clinical trial to collect MRI scans from various scanner manufacturers (General Electric, Siemens and Philips mainly), as is also the rule in the clinical practice. Although there are subtle technical differences in the implementation of each MRI pulse sequence, the outcome (e.g. the MR images) is extremely similar from a visual standpoint whatever the origin. This would therefore not introduce a bias in the analysis for qualitative assessments (bone disease scoring). For quantitative assessments (organ volumes), specific efforts are made when setting up the MRI protocol at each site in order to minimize the variability across sites, and allow accurate measurements.

When it comes to assessing longitudinal changes (either qualitatively or quantitatively), it is highly preferable to impose that the exact same scanner and scanning parameters be used from one visit to the other at a given site. Such requirement is reminded to the MRI facilities within the study imaging guidelines, and verified upon image QC at BioClinica.

4.12 Study Duration

The study is developed in conjunction with the French Referral Centers of Lysosomal Diseases, and the French Gaucher Treatment and Evaluation Committee (CETG: Comité d'Evaluation du Traitement de la maladie de Gaucher). It is a retro prospective observational study of the French cohort of patients with type 1 Gaucher disease treated with VPRIV® in everyday clinical practice.

It consists of two phases: a retrospective and a prospective phase with a 1 year inclusion period.

Phase I: retrospective phase

The retrospective period includes the period between the date of the baseline MRI to the patient's date of inclusion in the study. The reference MRI is defined as the closest MRI to the initiation of VPRIV®, within the past five years, or within three months after initiation of VPRIV®.

Phase II: prospective phase

Prospective period will be one year from the date of patient inclusion in the study.

The final MRI

MRI being performed in current practice every 2 years, the final MRI follow-up performed corresponds to those in the previous year or in the year following the patient's inclusion.

The duration of the study will be 2 years: a 1-year inclusion period to be sure to include all patients treated with VPRIV® (reviewed annually in consultation each year) and a prospective follow-up period of 1 year.

Provisional timetable for the study:

CCTIRS / CNIL authorization	October 23, 2015
Inclusion of the first patient in the study	September 30, 2016
Inclusion of the last patient in the study	September 30, 2017
Last visit of the last patient	September 30, 2018
Study clinical report	January 31, 2019

5 STUDY POPULATION

To reflect the daily practices, this study includes all patients with a confirmed diagnosis of Type 1 Gaucher disease treated with VPRIV® at the date of beginning of the study and who meet the selection criteria of the study.

5.1 Inclusion Criteria

1. Patients of any age or gender with confirmed diagnosis of type 1 Gaucher disease,
2. Patients treated with VPRIV® at the beginning of the study. Prior starting VPRIV® patients could be either treatment naïve or previously treated with any other Gaucher treatment than VPRIV®.
3. Patients should have one MRI data in the 5 previous years before starting VPRIV® treatment
4. Informed written consent obtained from the patient, and/or patient's parent(s), and/or legal representative. Assent, if old enough to grant, will be obtained from all patients under the age of 18 years.

5.2 Exclusion Criteria

1. Patients for whom MRI is contra-indicated
2. Patients who did not had an MRI during the five years prior to the initiation of treatment with VPRIV® or within three months after initiation of VPRIV®
3. Patients included in an ongoing clinical trial where the product is blinded

5.3 Withdrawal of Patients from the Study

Patients are free to withdraw from the study at any time without having to justify their decision and without any consequences for their quality of care and the quality of their relation with their treating physician. However, if possible the reason of the withdrawal will be asked and recorded.

6 STUDY PROCEDURES

6.1 Informed Consent

It is the responsibility of the Investigator to obtain written Informed Consent and assent, where applicable from study patients. All consent and assent documentation must be in accordance with applicable regulations and GCP. Each patient or the patient's legally authorised representative as applicable is requested to sign the Patient Informed Consent

Form or a certified translation, if applicable after the patient has received and read (or been read) the written patient information and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences and the patient's rights and responsibilities. A copy of the informed consent and assent documentation (i.e., a complete set of patient information sheets and fully executed signature pages) must be given to the patient or the patient's legally authorised representative. If applicable, it is provided in a certified translation of the local language. Signed consent forms must remain in each patient's study file and must be available for verification at any time.

The Principal Investigator provides the Sponsor with a copy of the consent form (and assent form where applicable) which was reviewed by the IRB/IEC and which received their favourable opinion/approval. A copy of the IRB/IEC's written favourable opinion/approval of these documents must be provided to the Sponsor, prior to the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national provisions) prior to study start that another party (i.e., sponsor or Coordinating Principal Investigator) is responsible for this action. Additionally, if the IRB/IEC requires modification of the sample, Patient Information and Consent document provided by the Sponsor, the documentation supporting this requirement must be provided to the Sponsor.

6.2 Institutional Review Board or Independent Ethics Committee

For investigator sites outside the EU, it is the responsibility of the Investigator to submit this protocol, the informed consent document (approved by the Sponsor or their designee), relevant supporting information and all types of patient recruitment information to the IRB/IEC for review, and all must be approved prior to site initiation.

For investigator sites within the EU and if applicable within a given region the applicant for an IEC opinion can be the Sponsor, the Investigator, or for multicentre studies the Coordinating Principal Investigator or Sponsor, according to national provisions.

Responsibility for coordinating with IRBs/IECs is defined in the Investigator/Sponsor (CRO) Contract.

Prior to implementing changes in the study, the Sponsor and the IRB/IEC must approve any revisions of any revised informed consent documents and amendments to the protocol unless there is a patient safety issue.

For investigator sites outside the EU, the Investigator is responsible for keeping the IRB/IEC apprised of the progress of the study and of any changes made to the protocol, but in any case at least once a year. For investigator sites within the EU and if applicable within a given region, this can be done by the Sponsor, the Investigator or for multicentre studies the Coordinating Principal Investigator, according to national provisions. The Investigator must also keep the local IRB/IEC informed of any serious and significant AEs.

6.3 Study Entrance Criteria

At screening, each patient will be reviewed for eligibility against the study entrance criteria. Patients who do not meet the study entrance criteria will not be allowed to participate in the study. The reason(s) for the patient's ineligibility for the study will be reviewed during remote and/or on-site monitoring visits (investigating the number of patients expected at the site vs. the number observed in the database).

6.4 Confirmation of Study Eligibility

Patient eligibility according to the study inclusion and exclusion criteria will be confirmed at Baseline on the basis of review of the study entrance criteria.

6.5 Demographics

Patient demographic information including gender, age, and professional status will be collected as soon as the patient is included in the observational study. The age that will be collected is the age of patient at VPRIV® treatment initiation.

6.6 Medical History

For the retrospective part of the study, medical past history are collected by the physician from the medical record of the patient. On the CRF are reported:

- Socio-demographic and clinical characteristics of patients with Gaucher's disease
- All medical past history of the patient: nature, beginning date, end date or ongoing and relationship to Gaucher disease
- Family past history : nature and family link
- The description of the history of the disease : year of first symptoms, nature of the first symptoms, diagnostic year, nature of the laboratory examination which has confirmed the diagnosis (enzyme assay, molecular biology (genotyping), bone marrow, bone marrow biopsy, liver biopsy, histology of the spleen, other), value of the enzyme assay, phenotype and genotype
- The clinical and biological status within the 6 months period : 3 months before the MRI - 3 months after the selected MRI which is the closest available one to the VPRIV® initiation
- The clinical and biological status of the patients when the VPRIV® treatment was initiated
- The standardized measures issued from the standardized review of the MRI by Bioclinica centralized laboratory. The review is conducted on the MRI that the treating physician addresses via the CETG to a central review radiological center after anonymisation of the documents

The quality of the MRI is evaluated and classified in three categories: Optimal, sub optimal and not assessable according the following definition:

- Optimal: Sufficient anatomical coverage, good image quality with no to minimal image artifacts and compliance with the imaging protocol
- Suboptimal: Sufficient anatomical coverage, presence of moderate image artifacts and/or minor deviations to the imaging protocol, with minimal impact on the analysis

- Not assessable: Insufficient anatomical coverage and/or presence of strong image artifacts and/or severe deviations to the imaging protocol, which would lead to an unreliable analysis.

Spleen/Liver:

TEST	DESCRIPTION	FORMAT/VALUES
ABDO_TECH_AD	Technical Adequacy for Abdominal MR data	0 = Optimal 1 = sub optimal 2 = Not assessable
ABDO_TECH_REASONS	Reasons for Abdominal MR images not being optimal	List of reasons separated by a
SPLEEN_VOL	Spleen Volume (mm3)	FLOAT
LIVER_VOL	Liver Volume (mm3)	FLOAT
SPLEEN_COV	Full Spleen Coverage achieved	Y/N
LIVER_COV	Full Liver Coverage achieved	Y/N
SPLEEN_INF	Presence of Infarcts	Y/N
SPLEEN_FD	Presence of Filling Defects	Y/N
LIVER_INF	Presence of Infarcts	Y/N
LIVER_FD	Presence of Filling Defects	Y/N

Spine/Femur:

TEST	DESCRIPTION	FORMAT/VALUES
SPINE_TECH_AD	Technical Adequacy for Spine MR data	0 = Optimal 1 = sub optimal 2 = Not assessable
SPINE_TECH_REASONS	Reasons for Spine MR images not being optimal	List of reasons separated by a
SPINE_BMB_T1	Spine BMB score of T1-weighted	0 = Slightly hyper intense 1 = Isointense 2 = Slightly hypo intense 3 = Hypo intense 4 = N/A
SPINE_BMB_T2	Spine BMB score of T2-weighted	0 = Iso intense 1 = Slightly hypo intense 2 = Slightly hyper intense 3 = Hypo intense 4 = Hyper intense 5 = N/A

Retrospective and prospective observational study of MRI changes in bone and visceral lesions of patients with type 1 Gaucher disease treated with VPRIV® (velaglucerase alfa)

SPINE_BMB_INFILTR	Spine BMB score for Infiltration Pattern	0 = None 1 = Patchy 2 = Diffuse 5 = N/A
SPINE_BMB_FAT	Assessment of Spinal Fat in Basivertebral Region	3 = Preservation of fat 4 = Absence of fat 5 = N/A
SPINE_COMMENTS	Free Comments on Spine Scoring	
FEMUR_TECH_AD	Technical Adequacy For Femur MR Data	0 = Optimal 1 = Readable, but not optimal 2 = Not readable
FEMUR_TECH_REASONS	Reasons for Femur MR images not being Optimal	List of reasons separated by a
FEMUR_BMB_T1	Femur BMB Score of T1-weighted	0 = Slightly hyper intense or isointense 1 = Slightly hypo intense 2 = Hypo intense 3 = N/A
FEMUR_BMB_T2	Femur BMB Score of T2-weighted	0 = Isointense 1 = Slightly hypo intense 2 = Slightly hyper intense 3 = Hypo intense 4 = Hyper intense 5 = Mixed type 6 = N/A
FEMUR_BMB_SITE	Femur BMB Score for sites of involvement	0 = No site of involvement 1 = Diaphysis 2 = Proximal epiphysis / apophysis 3 = Distal epiphysis 4 = N/A
FEMUR_COMMENTS	Free comments on Femur scoring	

Posology at initiation: UI/kg/2 weeks, UI/kg/3 weeks, UI/kg/1month

6.7 Efficacy and Effectiveness Assessments

For the closest MRI realized before the initiation of VPRIV® treatment and for each MRI which will be conducted during the prospective one year period, the following information will be recorded whenever they are available in patient's dossiers. Clinical and biological status will also be recorded when treatment was started and the patient included in the study.

- Spine and femur BMB score of T1 and T2 weighted,
- Marrow infiltration, bone infarction, osteonecrosis, pathological fractures (vertebral)

The clinical status:

- Height, weight
- Asthenia (absent / present : mild , moderate or severe), abdominal pain (absent / present : mild , moderate or severe), chronic pain in bone (absent / present : mild , moderate or severe), hemorrhagic syndrome (epistaxis, gingival bleeding, bruising, other rated : absent / present : mild , moderate or severe), lung disease, neurological disease

The biological status:

hemoglobin (g/dl); leukocytes (cells/mm³); platelets (mm³); ACE (angiotensin converting enzyme (U/l); ferritin (mg/l); chitotriosidase (nmol / h / ml); CCL18 (ng/ml), vitamin D (nmol/l), vitamin B12 (pmol/l); SGOT/AST (U/l), SGPT/ALT (U/l), GGT (U/l), alkaline phosphatase (U/l), triglycerides (mmol / l), total cholesterol (mmol/l) gamma globulin (g/l) serum calcium (mmol/l) presence or absence of a monoclonal peak and type if any.

The review will be done on the MRI that the treating physician has addressed for a central review radiological center via the CETG after blinding of the documents.

As previously, the quality of the MRI is evaluated and classified in three categories: Optimal, sub optimal and not assessable according the following definition:

- Optimal: Sufficient anatomical coverage, good image quality with no to minimal image artifacts and compliance with the imaging protocol
- Suboptimal: Sufficient anatomical coverage, presence of moderate image artifacts and/or minor deviations to the imaging protocol, with minimal impact on the analysis
- Not assessable: Insufficient anatomical coverage and/or presence of strong image artifacts and/or severe deviations to the imaging protocol, which would lead to an unreliable analysis.

Spleen/Liver:

TEST	DESCRIPTION	FORMAT/VALUES
ABDO_TECH_AD	Technical Adequacy for Abdominal MRI data	0 = Optimal 1 = Sub optimal 2 = Not assessable
ABDO_TECH_REASONS	Reasons for Abdominal MR images not being optimal	List of reasons separated by a
SPLEEN_VOL	Spleen volume (mm3)	FLOAT
LIVER_VOL	Liver Volume (mm3)	FLOAT
SPLEEN_COV	Full Spleen Coverage achieved	Y/N
LIVER_COV	Full Liver Coverage achieved	Y/N
SPLEEN_INF	Presence of Infarcts	Y/N

Retrospective and prospective observational study of MRI changes in bone and visceral lesions of patients with type 1 Gaucher disease treated with VPRIV® (velaglucerase alfa)

TEST	DESCRIPTION	FORMAT/VALUES
SPLEEN_FD	Presence of Filling Defects	Y/N
LIVER_INF	Presence of Infarcts	Y/N
LIVER_FD	Presence of Filling Defects	Y/N

Spine/Femur:

TEST	DESCRIPTION	FORMAT/VALUES
SPINE_TECH_AD	Technical Adequacy for Spine MR data	0 = Optimal 1 = sub optimal 2 = Not assessable
SPINE_TECH_REASONS	Reasons for spine MR images not being optimal	List of reasons separated by a
SPINE_BMB_T1	Spine BMB score of T1-weighted	0 = Slightly hyper intense 1 = Iso intense 2 = Slightly hypo intense 3 = Hypo intense 4 = N/A
SPINE_BMB_T2	Spine BMB score of T2-weighted	0 = Isointense 1 = Slightly hypo intense 2 = Slightly hyper intense 3 = Hypo intense 4 = Hyper intense 5 = N/A
SPINE_BMB_INFILTR	Spine BMB score for Infiltration Pattern	0 = None 1 = Patchy 2 = Diffuse 5 = N/A
SPINE_BMB_FAT	Assessment of Spinal Fat in Basi vertebral Region	3 = Preservation of fat 4 = Absence of fat 5 = N/A
SPINE_COMMENTS	Free Comments on Spine Scoring	
FEMUR_TECH_AD	Technical Adequacy for Femur MR data	0 = Optimal 1 = Readable, but not optimal 2 = Not readable
FEMUR_TECH_REASONS	Reasons for Femur MR images not being optimal	List of reasons separated by a
FEMUR_BMB_T1	Femur BMB score of T1-weighted	0 = Slightly hyper intense or isointense 1 = Slightly hypo intense 2 = Hypo intense 3 = N/A
FEMUR_BMB_T2	Femur BMB score of T2-weighted	0 = Isointense 1 = Slightly hypo intense

		2 = Slightly hyper intense 3 = Hypo intense 4 = Hyper intense 5 = Mixed type 6 = N/A
FEMUR_BMB_SITE	Femur BMB score for sites of involvement	0 = No site of involvement 1 = Diaphysis 2 = Proximal epiphysis / apophysis 3 = Distal epiphysis 4 = N/A
FEMUR_COMMENTS	Free comments on femur scoring	

6.8 Safety Assessments

Safety of VPRIV® will be assessed according to ADRs, safety reporting associated with any medication given according to clinical routine. It should also be done according to local applicable drug law and using the procedures of the respective pharmaceutical manufacture.

6.9 Concomitant Medications, Therapies, and Medical/Surgical Interventions Assessments

All medications, therapies/interventions administered to and medical/surgical procedures performed on the study subjects from the time of informed consent through the follow-up contact are regarded as concomitant and will be documented on the CRF.

6.10 Adverse Events Assessments

Definition of Adverse Events/Adverse Drug Reactions, Period of Observation, Recording of Adverse Events/Adverse Drug Reactions

An **Adverse Event** (AE) is any untoward medical occurrence in a clinical investigation patient administered a product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, disease or exacerbation of a pre-existing condition temporally associated with the use of a medicinal product.

Only AEs that will appear only in the prospective part of this observational study and which are considered to be related to Velaglucerase alpha are considered as ADRs, will be collected during this study, ADRs that will be related to the retrospective part of this study will not be collected. (See Section 7.1.2 for further guidance). An ADR is a response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, and therapy of disease or for the restoration, correction, or modification of physiological function. Response in this context means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility. Each ADR requires a complete and thorough description on the CRF.

All ADRs, including those associated with the protocol are collected from the time the informed consent is signed until the end of the study duration, are to be recorded on the

appropriate CRF and in source documents. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made then each symptom should be listed individually.

All ADRs (serious and non-serious) must be followed until closure (the patient's health has returned to his/her baseline status or all variables have returned to normal), an outcome is reached, stabilization (the Investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained regardless of whether or not the patient is still participating in the study. When appropriate, medical tests and examinations are performed so that resolution of event(s) can be documented.

Severity Categorisation

The severity of AEs must be recorded during the course of the event including the start and stop dates for each severity. An event that changes in intensity should be captured as a new event. Worsening of pre-treatment events, must be recorded as new AEs (for example if a patient experiences mild intermittent dyspepsia prior to dosing, but the dyspepsia becomes severe and more frequent after first dose of product administration, a new AE of severe dyspepsia (with the appropriate date of onset) is recorded on the appropriate CRF).

The medical assessment of intensity is determined by using the following definitions:

Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: A type of AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research patient.

Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Relationship Categorisation

An Investigator who is qualified in medicine must make the assessment of relationship to product for each AE. The Investigator should decide whether, in his or her medical judgement, there is a reasonable possibility that the event may have been caused by the product. If there is no valid reason for suggesting a relationship, then the AE should be classified as 'not related'. Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the product and the occurrence of the AE, then the AE should be considered 'related'.

The following additional guidance may be helpful:

Term	Relationship	Definition
Related	Yes	The temporal relationship between the event and the administration of the product is compelling and/or follows a known or suspected response pattern to that product, and the event cannot be explained by the patient's medical condition, other therapies, or accident.
Not Related	No	The event can be readily explained by other factors such as the patient's underlying medical condition, concomitant therapy or accident and no obvious temporal or biologic relationship exists between the product and the event.

Outcome Categorisation

The outcome of AEs must be recorded during the course of the study in the CRF. Outcomes are as follows:

- Fatal
- Not Recovered/Not Resolved
- Recovered/Resolved
- Recovered/Resolved With Sequelae
- Recovering/Resolving
- Unknown

Symptoms of the Disease under Study

Symptoms of the disease under study should not be classed as ADRs as long as they are within the normal day-to-day fluctuation or expected progression of the disease. However, significant worsening of the symptoms should be recorded as an ADR.

Clinical Laboratory Evaluations

A change in the value of a safety laboratory investigation can represent an ADR if the change is clinically relevant or if, during treatment with the product, a shift of a parameter is observed from a normal value to an abnormal value, or a further worsening of an already abnormal value which is assessed to be associated with the use of VPRIV®. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing treatment or after the end of treatment with the product, and the range of variation of the respective parameter within its reference range, must be taken into consideration.

If, at the end of the observation period, there are abnormal laboratory values which were not present at the time of informed consent/patient enrolment, further clinical or laboratory investigations should be

performed until the values return to within reference range or until a plausible explanation (e.g., concomitant disease) is found for the pathological laboratory values.

The Investigator should decide, based on the above criteria and the clinical condition of a patient, whether a change in a laboratory parameter is clinically significant and therefore represents an AE.

Pregnancy

All pregnancies are to be reported from the time informed consent is signed until the end of the study duration, as applicable.

Any report of pregnancy for any female study participant must be reported within one business day to Shire Pharmacovigilance Department using the Shire Pharmaceuticals Investigational and Marketed Products Pregnancy Form.

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the Investigator to obtain this information within 30 calendar days after the initial notification and approximately 30 calendar days post-partum. If no information is received, 1 additional documented follow-up attempt will be made approximately 30 calendar days after the 30-day post-partum contact.

Pregnancy complications such as miscarriage or congenital abnormality are considered SAEs and must be reported using the Shire Pharmaceuticals Clinical Trial Serious Adverse Event Report Form. An elective abortion, which is not associated with any complications, in itself, does not meet the criteria of an SAE.

If the Investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE using the Shire Pharmaceuticals Clinical Trial Serious Adverse Event Report Form. The test date of the first positive serum/UA HCG test or ultrasound result will determine the pregnancy onset date.

Abuse, Misuse, Overdose and Medication Errors

Abuse, misuse, overdose or medication error must be reported to the Sponsor according to the SAE reporting procedure whether or not they result in an AE/SAE as defined in Section 7.2.

- **Abuse** – Persistent or sporadic intentional intake of a product at higher dose than prescribed per protocol (but below the dose defined for overdose) or when used for non-medical purpose (e.g. altering one's state of consciousness).
- **Misuse** – Intentional or un-intentional use of a product other than as directed or indicated at any dose which is at or below the dose defined for overdose (Note: this includes a situation where the test article is not used as directed at the dose prescribed by the protocol).
- **Overdose** – Intentional or un-intentional intake of a dose of a product higher than dosage levels described in the label for VPRIV®.
- **Medication Error** – A mistake made in prescribing, dispensing, administration, and/or use of the product.

6.11 Serious Adverse Drug Reactions

All SADR are collected and reported to Shire Pharmacovigilance.

The reference for safety information for this study is available in the French VPRIV® SmPC.

A **Serious Adverse Drug Reaction (SADR)** is any untoward medical occurrence considered to be related to VPRIV® at any dose:

- Results in death
- Is life-threatening

NOTE: The term ‘life-threatening’ in the definition of ‘serious’ refers to an event in which the subject 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 was more severe.

- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect
- Is an Important Medical Event; Note: Important Medical Events that may not result in death, be life-threatening, or require hospitalisation may be considered an SADR when, based upon appropriate medical judgment, they may jeopardise the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in this definition. In addition, suspected transmission (via marketed medicinal product) of any infectious agent is reportable to the Sponsor.

Examples of important medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalisation; or development of drug dependency or drug abuse.

Hospitalisations, which are the result of elective or previously scheduled surgery for pre-existing conditions, which have not worsened after initiation of treatment, should not be classed as SADRs. For example, an admission for a previously scheduled ventral hernia repair would not be classed as SADRs; however, complication(s) resulting from a hospitalisation for an elective or previously scheduled surgery that meets the serious criteria must be reported if it qualifies as an SADR.

All SADRs are to be collected from the time the patient signs informed consent until the end of the 6-month study duration and it must be reported to the Sponsor/designee within 1 business day of the first awareness of the event.

The onset date of the SADR is defined as the date the event met serious criteria and the resolution date is defined as the date the event no longer met serious criteria, when the symptoms resolve, or the event is considered chronic or closed (i.e., when no further information is expected). In the case of hospitalisations, the hospital admission and discharge dates would be considered the onset and resolution dates, respectively.

Additionally, any signs or symptoms experienced by the patient prior to admission into the hospital or leading up to the onset date of the SADR and following the resolution date of the SADR, must be recorded as an ADR as appropriate, to identify individual seriousness and intensities.

Any SAE that results in the patient’s death (i.e., the SAE was noted as the primary cause of death) must have fatal checked as an outcome and the resolution date for that event is the date of death. For all other

events ongoing at time of death that did not contribute to the patient's death, the outcome should be considered not resolved, without a resolution date recorded.

The physician/investigator is responsible to:

- Report all SADRs to Shire Pharmacovigilance department within one business day of the first awareness of the event.
- Complete, sign and date the Shire Clinical Trial Serious Adverse Event Form, verify the accuracy of the information recorded on the Shire Clinical Trial SAE Form with the corresponding source documents, and send a copy by fax to: (+44 (0)1256 894715 or +33 (0) 1 46 08 21 49) or email (globalpharmacovigilance@shire.com) to the Shire Pharmacovigilance department.
- Notify, according to the local laws and requirements, any ethics committees (as applicable) and/or regulatory agencies, of:
 - SADRs that occur at his or her site, as required
 - All unexpected SADRs (15 Day Safety Reports) that occur during clinical trials with VPRIV®.

The physician/investigator is encouraged to discuss with Shire's Medical Monitor any ADRs for which the issue of relationship is unclear or questioned. Multiple inquiries between the Sponsor and/or the CRO and the study site may be necessary for report preparation.

The **Sponsor** must:

- Notify the relevant regulatory authorities/EU central Independent Ethics Committees (IEC) of unexpected SADRs
- Notify investigators of new relevant safety information that becomes available during any studies with VPRIV®

6.12 Removal of Patients from the Study

A patient's participation in the study may be discontinued at any time at the discretion of the Investigator. The following may be justifiable reasons for the Investigator to remove a patient from the study:

- Non-compliance, including failure to appear at one or more visits (or standard of care)
- The patient was erroneously included in the study
- The patient develops an exclusion criterion
- The patient suffers an intolerable adverse event
- The study is terminated by the Sponsor

The patient, the patient's parent(s), or the patient's legally authorized representative acting on behalf of the patient is free to withdraw consent and discontinue participation in the study at any time without prejudice to further treatment by the physician or at the institution. Discontinued patients should be followed according to medical practice standards.

If a patient or the patient's parent(s) or the patient's legally authorized representative(s) acting on behalf of the patient, discontinues participation in the study, or the patient is discontinued by the Investigator,

Retrospective and prospective observational study of MRI changes in bone and visceral lesions of patients with type 1 Gaucher disease treated with VPRIV® (velaglucerase alfa)

reasonable efforts will be made to follow the patient through the end of study assessments. The reason for refusal will be documented on the eCRF. Any adverse events (AE's) experienced up to the point of discontinuation must be documented on the AE eCRF. If AEs are present when the patient withdraws from the study, the patient will be re-evaluated within 30 days of withdrawal. All ongoing SAEs at the time of withdrawal will be followed until resolution.

7 QUALITY CONTROL AND ASSURANCE

7.1 Appropriateness of Measurements

- MRI is a standard method to study the evolution of the bones, liver and spleen impairment, the only difference with the standard practice is that a second review of all document will be conducted in a central review center in order to have standardized measurement. Patients for whom MRI is contraindicated are excluded from the study.

Training will occur at an Investigator meeting or at the site initiation visit or both, and instruction manuals will be provided to aid consistency in data collection and reporting across sites.

7.2 Monitoring

Clinical sites will be monitored by the Sponsor or its designee to ensure the accuracy of data against source documents. The required data will be captured in a validated clinical data management system that is compliant with the FDA 21 CFR Part 11 Guidance and other global guidances as required. The clinical study database will include an audit trail to document any evidence of data processing or activity on each data field by each user. Users will be trained and given restricted access, based on their role(s) in the study, through a password-protected environment.

Data entered in the system will be reviewed manually for validity and completeness against the source documents by a clinical monitor from the Sponsor or its designee. If necessary, the study site will be contacted for corrections or clarifications; all missing data will be accounted for.

Serious adverse event information captured in the clinical study database will be reconciled with the information captured in the Pharmacovigilance and Risk Management database.

8 PLANNED STATISTICAL METHODS

8.1 General Considerations

Statistical plan will be written and Statistical analysis will be conducted by CenBiotech using SAS 9.3 and under the authority of Pr Francois-André Allaert, Public health specialist and biostatistician, head of the medical evaluation Chair of the Business school of Dijon. A detailed analysis plan will be secondary provided and validated by Shire.

8.2 Determination of Sample Size

There is no predefined sample size but in order to reflect daily practices, the study may include all patients presenting type 1 Gaucher disease and treated with VPRIV® in France. So, based on data from the CETG, a sample size from 40 to 50 patients could be expected.

8.3 Analysis Populations

All patients included in the study will be included in the statistical analysis

8.4 Demographics and Baseline Characteristics

The socio-demographic and clinical characteristics of the cohort of patients with type 1 Gaucher's disease and the arrangements for their care are described by the usual parameters, mean and standard deviation for quantitative variables, frequencies and percentages for qualitative variables.

8.5 Primary Endpoint(s) or Assessments

The changes pre and post treatment with velaglucerase alfa of the spine and femur BMB score will be described and compared using Wilcoxon signed-rank test. The analysis will be conducted successively on all MRI assessable and on optimal quality MRI only.

Primary Safety Endpoint(s)

Adverse events will be coded using MedDRA and described as recommended in ECH procedures as far as possible due in particular to retrospective conditions..

Primary Efficacy/Effectiveness Endpoint(s)

The values observed at the different follow up times and the variations between the reference MRI and the follow-up MRI, of the BMB weighted score at T1 and T2 measured at the femur and lumbar spine, are described by mean and standard deviation and the 95% confidence interval will be calculated. These values will be compared at the different follow up times with test on repeated data: ANOVA on repeated series or Wilcoxon rank test, depending on the nature and distributions of the studied variables.

8.6 Secondary Endpoint(s)

The socio-demographic characteristics of the patients, the history of their disease, the context of the diagnosis, the medical history, the clinical evaluation criteria of liver and spleen, the MRI evaluation criteria of the liver and spleen, the MRI evaluation criteria of bone lesions and the biological evaluation criteria are described by mean and standard deviation for quantitative variables, by frequency and percentage for categorical and ordinal variables. The 95% confidence intervals will be calculated. The evolutions of these criteria at the different periods when they are collected are described by mean and standard deviation or percentage changes. They are compared between the different times of the study by test on repeated data: ANOVA on repeated series or Wilcoxon rank test, depending on the nature and distributions of the studied variables

The analysis will describe and analyze the evolution of bone disease on the basis of the MRI's measures. It will describe and analyzes also the evolution of patients on the basis of their other MRI measures, clinical and laboratory data. It will describe also the incidence of spleen infarcts, fibrosis, liver nodules and their evolution under treatment by velaglucerase alfa.

Comparisons shall be made by analysis of variance on repeated series for quantitative variables or by Wilcoxon signed rank tests if normality is not demonstrated and by McNemar tests or rank tests on repeated series for quantitative or ordinal criteria

Changes over time in hepatomegaly, presence of lithiasis, nodules or infarct will be analysed using macNemar test and changes in liver measurements will be compare using analysis of variance on repeated series,

Changes over time in splenomegaly, presence of nodules or infarct will be analysed using Mac Nemar test and changes in spleen measurements will be compare using analysis of variance on repeated series,

Change in marrow infiltration, bone infarction, osteonecrosis, pathological fractures vertebral will be analysed using Mac Nemar test or Wilcoxon rank test.

Changes in fatigue, abdominal pain, bone pain: hemorrhagic syndrome, lung disease and neurological disease will be analysed using Mac Nemar test or wilcoxon rank test

Changes over time of biological parameters (hemoglobinemia, leucocytes, platelets count, SGOT, SGPT, Gamma GT, alkaline phosphatases, converting enzyme angiotensin, ferritin, chitriosidase, gamma globulins, IgG, IgA, IgM, calcium level, D vitamin, B12 vitamin, triglycerides, cholesterol, monoclonal peak) will be analysed using variance analysis on repeated series.

Logistic regression type shall be used to determine criteria influencing positive or negative evolutions. The analysis on MRI parameters will be conducted successively on all MRI assessable and on optimal quality MRI only.

8.7 Interim Analysis

All data analysis previously described will be conducted at the end of the study scheduled on February 2018.

9 ADMINISTRATIVE CONSIDERATIONS

9.1 Investigators and Study Administrative Structure

All the financial convention between Shire and the medical practitioners will be submitted for approval to the National Board of Medical Professional and declare to the French administrative authorities according the reference procedure.

The Investigator should ensure that all persons assisting with the study are adequately informed about the protocol, any amendments to the protocol, the study treatments, and their study related duties and functions. The Investigator must maintain a list of sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study related duties.

9.2 Institutional Review Board or Independent Ethics Committee Approval and Other Governing Regulatory Bodies

The protocol, the CRF and the informed consent of this observational study have be approved by the CCTIRS.

9.3 Study Monitoring

Good Pharmacoepidemiological (GPPs) guidelines for observational studies will be followed. Review of the eCRFs for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed.

The study will be monitored by the Sponsor or its designee. Monitoring will be performed by a representative of the Sponsor (Clinical Study Monitor) who will review the eCRFs and source documents. The site monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements by frequent site visits and communications (letter, telephone, and facsimile) and in accordance with current GPPs and the respective local and French government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

The Sponsor ensures that Local Regulatory Authority requirements are met before the start of the study. The Sponsor (or a nominated designee) is responsible for the preparation, submission, and confirmation of receipt of any Regulatory Authority approvals required.

9.4 Case Report Forms and Study Records

The clinical data are extracted from the medical record of the patients and are reported on the paper form. Forms are then transmitted by mail to the CRO which records it (double entry) on a computerized CRF developed on capture system. Automatic control of data entry and automatic request on missing data or data not fulfilling the control quality previously described in accordance with the laboratory are issued and transmitted to the medical practitioner

Case report forms (paper) are provided for each patient. All forms must be filled out by authorized study personnel. All corrections to the original CRF entry must indicate the reason for change. The Investigator is required to sign the CRF after all data have been captured for each patient. If

corrections are made after review and signature by the Investigator, he or she must be made aware of the changes, and his or her awareness documented by resigning the CRF.

9.5 Critical Documents

Before Shire Rare diseases initiates the study (ie, obtains written informed consent from the first patient), it is the responsibility of the Investigator to ensure that all required documents are available to Shire Rare diseases or their designee. Examples include:

- Curricula vitae of Investigator and sub-investigator(s) (current, dated and signed within 12 months of study initiation)
- Signed and dated agreement of the final protocol
- Signed and dated agreement of any amendment(s), if applicable
- Approval/favorable opinion from the CCTIRS and by the National Board of Medical Practitioner clearly identifying the documents reviewed by name, number and date of approval or re approval: protocol, any amendments, Subject Information/Informed Consent Form, and any other written information to be provided regarding subjects recruitment procedures
- Copy of CCTIRS approved Subject Information/Written Informed Consent Form/any other written information

Regulatory approval and notification as required must also be available; these are the responsibility of Shire Rare diseases.

9.6 Data Monitoring Committee and/or Adjudication Committee

Nadia Belmatoug MD, Service de Médecine Interne- Centre de Référence des maladies lysosomales, Hôpital Beaujon, Clichy, France

- David Petrover MD, hôpital Lariboisière, Clinique Bachaumont, Paris, France

- Luc Bracoud, Centre Bioclinica, Lyon, France

- François-André Allaert, MD, PhD, CHRU Bocage, Dijon, France

9.7 Protocol Violations/Deviations

The Investigator will conduct the study in compliance with the protocol. The protocol will not be initiated until the CCTIRS and the appropriate regulatory authorities have given approval/favorable opinion. Modifications to the protocol will not be made without agreement of the Sponsor. Changes to the protocol will require written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients.

The CCTIRS may provide, if applicable regulatory authorities permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval/favorable opinion of the CCTIRS. The Sponsor will submit all protocol modifications to the regulatory authorities in accordance with the governing regulations.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to patients, the Investigator will contact the Sponsor or its designee, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented as a protocol deviation.

Protocol deviations will need to be reviewed by the medical monitor and may also be required to be submitted to the CCTIRS.

Protocol modifications will only be initiated by the Sponsor and must be approved by the CCTIRS or other applicable international regulatory authority before initiation.

9.8 Premature Closure of the Study

If the Sponsor, Investigator, or regulatory authorities discover conditions arising during the study which indicate that the clinical investigation should be halted due to an unacceptable patient risk, the study may be terminated after appropriate consultation between the Sponsor and the Investigator(s). In addition, a decision on the part of the Sponsor to suspend or discontinue development of the product may be made at any time. Conditions that may warrant termination of the study or site include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study
- Failure of the Investigator to comply with pertinent global regulations
- Submission of knowingly false information from the study site to the Sponsor or other pertinent regulatory authorities
- Insufficient adherence by the Investigator to protocol requirements

9.9 Access to Source Documentation

Regulatory authorities, the IRB/IEC, or the Sponsor may request access to all source documents, CRFs, and other study documentation for onsite audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities. Monitoring and auditing procedures that comply with current GCP or GPP (where relevant) guidelines will be followed. On-site review of the CRFs for completeness and clarity, crosschecking with source documents, and clarification of administrative matters may be performed.

9.10 Data Generation and Analysis

The clinical database will be developed and maintained by Cenbiotech (a contract research organization) or an electronic data capture technology provider as designated by Shire Rare diseases. Cenbiotech will be responsible for performing study data management activities. Data will be recorded using double entry

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medication will be coded using WHO-Drug Dictionary (WHO-DD). Centralized laboratories will be employed as described in the study manual to aid in consistent measurement of efficacy and safety parameters.

9.11 Retention of Data

Essential documents should be retained until at least 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. The Sponsor will notify the Investigator if these documents must be retained for a longer period of time. It is the responsibility of the Sponsor to inform the Investigator or institution as to when these documents no longer need to be retained.

10 REFERENCE LIST

- 1) Maladie de gaucher. Protocole national de diagnostic et de soins, Haute Autorité de Santé, décembre 2015
- 2) Stirnemann J, et al, The French Gaucher's disease registry: clinical characteristics, complications and treatment of 562 patients, Orphanet J Rare Dis. 2012 Oct 9;7:77.
- 3) Javier RM, Hachulla E, Osteoarticular manifestations of Gaucher disease in adults: pathophysiology and treatment, 2007, Dec;36 (12 Pt 3):1971-84. Epub 2007 May 10
- 4) VPRIV Summary of Product Characteristics – Résumé des Caractéristiques Produit, http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/001249/human_med_001381.jsp&mid=WC0b01ac058001d124
- 5) Ben Turkia H, et al., Velaglucerase alfa enzyme replacement therapy compared with imiglucerase in patients with Gaucher disease, Am J Hematol 2013
- 6) Gonzalez DE et al. Enzyme replacement therapy with velaglucerase alfa in Gaucher disease: Results from a randomized, double-blind, multinational, Phase 3 study. Am J Hematol 2013;88:166–171
- 7) Zimran A, et al., therapy in adults with type 1 Gaucher disease: 48-month experience Phase 1/2 and extension study of velaglucerase alfa replacement, Blood 2010;115:4651–6
- 8) Zimran A et al. Safety and efficacy of velaglucerase alfa in Gaucher disease type 1 patients previously treated with imiglucerase. Am J Hematol 2013; 88: 172–178.
- 9) Elstein D, et al., Significant and continuous improvement in bone mineral density among type 1 Gaucher disease patients treated with velaglucerase alfa: 69-month experience, including dose reduction Blood Cells Mol Dis 2011; 47: 56–61.
- 10) Hughes DA, et al., Velaglucerase alfa (VPRIV) enzyme replacement therapy in patients with Gaucher disease: long-term data from phase III clinical trials, Am J Hematol 2015; 90: 584–91
- 11) Maas M, et al, Quantification of Bone Involvement in Gaucher Disease: MR Imaging Bone Marrow Burden Score as an Alternative to Dixon Quantitative Chemical Shift MR Imaging- Initial Experience, Radiology. 2003 Nov; 229(2): 554-61. Epub 2003 Oct 2.

Appendix 1 Protocol Amendment Summary of Changes

No amendment was made

Appendix 2 Overview of the Study Design

	0. Eligible patients (n= 40-50)	
	1. Patient inclusion (Written informed consent obtained)	
Retrospective data collection	<p>2. Retrospective data collection</p> <p><i>The closest MRI conducted during the 5 years before the initiation of VPRIV® treatment or in the 3 months after the VPRIV® initiation is collected and defined as the reference MRI.</i></p> <p><i>Clinical and biological data available 3 months before or after the reference MRI are collected</i></p> <p><i>Medical history and clinical and biological data available, when VPRIV® treatment is initiated, are collected</i></p> <p><i>Each MRI available since VPRIV® treatment initiation and patients inclusion is collected as well as clinical and biological data available 3 months before or after it</i></p> <p>.....</p> <p><i>MRI collected are anonymously sent to a central lab reading: MRI results data collection</i></p>	<p>Medical history</p> <p>Clinical data</p> <p>Laboratory data</p> <p>VPRIV® treatment</p> <p>MRI</p> <p>..... VPRIV treatment</p> <p>Centralized MRI reading:</p> <ul style="list-style-type: none"> - Liver and spleen volumes - BMB score of the spine and femur
Prospective data collection	<p>3. Prospective follow-up:</p> <p><i>For each MRI that will be conducted from the patient inclusion until the end of the one year follow up study, clinical and laboratory data available within the 3 months before the MRI and the 3 months after MRI are collected.</i></p> <p>.....</p> <p>.....</p> <p><i>MRI collected are anonymously sent to a central lab reading: MRI results data collection</i></p>	<p>Clinical data</p> <p>Laboratory data</p> <p>VPRIV® treatment</p> <p>MRI</p> <p>.....</p> <p>Centralized MRI reading:</p> <ul style="list-style-type: none"> - Liver and spleen volumes - BMB score of the spine and femur

Appendix 3 Protocol Signature Page

Study Title:

Retrospective and prospective observational study of patients with type 1 Gaucher disease treated with VPRIV® (velaglucerase alfa)

Study Number: RMGF - SHPGCB-703

Final Date: 05/04/2016

Amendment Date:

Sponsor's Approval

This study has been approved by Shire Rare diseases.

Signatory:
Sponsor



25/04/2016

Signature

Date

BESSA El Hadi

Printed Name

Investigator's Acknowledgement

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

Signatory:
Investigator
Name Title
Institution

Signature

Date

Printed Name

List of centers that will be involved in this study

Investigators/ centers	CENTRE DE COMPÉTENCE DES MALADIES HÉRÉDITAIRES DU MÉTABOLISME DU GRAND OUEST (Tours 1-2 - Angers - Poitiers)
	CENTRE DE PÉDIATRIE GATIEN DE CLOCHEVILLE 49 boulevard Béranger - 37044 Tours Cedex 09
	CHU TOURS - HÔPITAL BRETONNEAU 2 boulevard Tonnellé - 37044 Tours Cedex 09
	HÔPITAL JEANNE DE FLANDRE - CHRU DE LILLE Rue Eugène Avinée - 59037 Lille cedex
	HÔPITAL JEANNE DE FLANDRE Correspondant extra-hospitalier Hôpital Saint-Vincent Boulevard de Bellefort - 59020 Lille cedex
	HÔPITAL HURIEZ Correspondant extra-hospitalier Hôpital Huriez rue Michel Polonovski - 59100 Lille cedex
	HÔPITAL D'ENFANTS LA TIMONE 264 rue Saint Pierre - 13005 Marseille
	CHU DE REIMS - HÔPITAL ROBERT DEBRÉ Avenue du Général Koenig - 51092 Reims
	HÔPITAL HAUTEPIERRE 1 avenue Molière - 67098 Strasbourg
	HÔPITAL AUGUSTIN MORVAN 5 avenue Hoche - BP 824 - 29609 Brest Cedex
	CHU DE NANTES 38 boulevard Jean Monnet - 44093 Nantes
	HÔPITAL ARNAUD DE VILLENEUVE 371 avenue du Doyen Gaston Giraud - 34295 Montpellier cedex 05
	HÔPITAL LAPEYRONIE 371 avenue du Doyen Gaston Giraud - 34295 Montpellier cedex
	HÔPITAL GUI DE CHAULIAC Avenue Augustin Fliche - 34295 Montpellier cedex
	HÔPITAL FEMME-MÈRE-ENFANT/GROUPEMENT HOSPITALIER EST 59 boulevard Pinel - 69677 Bron cedex
	HÔPITAL D'ENFANTS LA TIMONE 264 rue Saint Pierre - 13005 Marseille
	HÔPITAL D'ENFANTS Rue du Morvan - 54511 Vandoeuvre-les-Nancy cedex
	HÔPITAL DE BRABOIS Allée du Morvan - 54511 Vandoeuvre-les-Nancy cedex
	HÔPITAL PELLEGRIN - CHU BORDEAUX Place Amélie Raba Léon - 33076 Bordeaux Cedex
	CHU LE BOCAGE Boulevard Maréchal De Lattre de Tassigny
	Centre national de référence de la maladie de Fabry et des maladies héréditaires du tissu conjonctif 104 boulevard Raymond Poincaré - 92380 Garches
	CHU SAINT-JACQUES ET JEAN MINJOZ 2 place Saint-Jacques et 1 boulevard Flemming - 25000 Besançon
	HÔPITAL BICHAT 46 rue Henri Huchard - 75018 Paris
	HÔPITAL COCHIN

Retrospective and prospective observational study of MRI changes in bone and visceral lesions of patients with type 1 Gaucher disease treated with VPRIV® (velaglucerase alfa)

27 rue du Faubourg Saint-Jacques - 75679 Paris cedex 14

GROUPE HOSPITALIER LA PITIÉ SALPÊTRIÈRE

47-83 boulevard de l'Hôpital - 75651 Paris cedex 13

HÔPITAL JEAN VERDIER

Avenue du 14 juillet - 93140 Bondy cedex

HÔPITAL TROUSSEAU

26 avenue du Docteur Arnold Netter - 75571 Paris cedex 12

HÔPITAL ROBERT DEBRÉ

48 boulevard Sérurier - 75019 Paris

HÔPITAL NECKER ENFANTS MALADES

149 rue de Sèvres - 75743 Paris cedex 15

GROUPE HOSPITALIER LA PITIÉ SALPÊTRIÈRE

47-83 boulevard de l'Hôpital - 75651 Paris cedex 13

HÔPITAL KREMLIN BICÊTRE

78 avenue du Général Leclerc - 94275 Le Kremlin Bicêtre

CHU DE REIMS - HÔPITAL ROBERT DEBRÉ

Avenue du Général Koenig - 51092 Reims