Cross-sectional, multicentre, non-interventional study to assess Giant Cell Arteritis medical practices in France

Artemis Study

Protocol

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SPONSOR

CHUGAI PHARMA FRANCE
Tour Franklin - Arche Sud
100/101 quartier Boieldieu
92042 Paris La Défense cedex

Tel: +33 1 56 37 05 20
Fax: +33 1 56 37 05 40

STUDY MANAGER

Dr Isabelle IDIER
Senior Medical Manager
Tel: +33 1 56 37 44 89
Mobile: +33 6 24 55 62 00
Fax: +33 1 56 37 05 40

CRO (monitoring, data processing, statistical analysis and medical writing)
ITEC Services
ZI Jean ZAY
3, avenue Georges Clémenceau
33150 CENON
FRANCE
Tel: +33 5 57 77 85 00
Fax: +33 5 57 77 85 01

SPONSOR SIGNATORIES OF THE PROTOCOL

The signatories attest that the Protocol Version 1.2 dated 20/06/2018, the CRF and appendices contain the information and recommendations required for the conduct of the study. The study will be carried out and recorded in accordance with this Protocol and Good Epidemiological Practice. Any amendment to the Protocol will require agreement from the signatories and will be documented in writing.

SPONSOR
Dr Thierry GUILLOT
CHUGAI PHARMA FRANCE
Tour Franklin - Arche Sud
100/101 quartier Boieldieu
92042 Paris La Défense cedex

Date: _____

Signature: _____

STUDY MANAGER
Dr Isabelle IDIER
CHUGAI PHARMA FRANCE
Tour Franklin - Arche Sud
100/101 quartier Boieldieu
92042 Paris La Défense cedex

Date:

Signature: _____

SCIENTIFIC COMMITTEE

Pr Valerie Devauchelle-Pensec
Rheumatology Department
CHU LA CAVALE BLANCHE,
Boulevard Tanguy Prigent
29609 BREST CEDEX 2
FRANCE
Email : valerie.devauchelle-pensec@chu-brest.fr

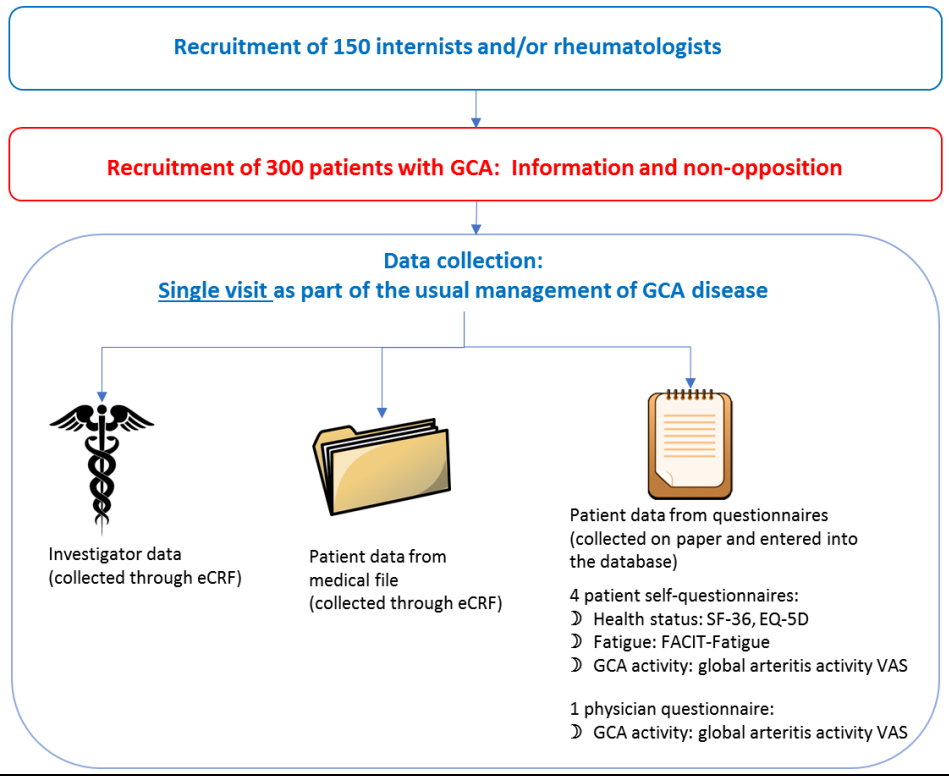
Pr Eric Hachulla
Internal Medicine Department
CHRU LILLE,
2 Avenue Oscar Lambret
59000 LILLE
FRANCE
Email : Eric.HACHULLA@CHRU-LILLE.FR

Pr Alfred Mahr
(Coordinator Investigator)
Internal Medicine Department
HOPITAL SAINT LOUIS,
1 Avenue Claude Vellefaux
75010 PARIS
FRANCE
Email : alfred.mahr@aphp.fr

Pr Marc Paccalin
Internal Medicine and Geriatic Medicine Department
CHU LA MILETRIE,
2 Rue de la Miletrie
86021 POITIERS CEDEX
FRANCE
Email : Marc.PACCALIN@chu-poitiers.fr

PROTOCOL SUMMARY

Study title	Cross-sectional, multicentre, non-interventional study to assess Giant Cell Arteritis medical practices in France
Population	Patients with giant cell arteritis (GCA)
Study rationale	GCA - also known as temporal arteritis, cranial arteritis, or Horton's disease - is a form of immune-mediated inflammatory systemic vasculitis that affects large and medium-sized arteries, predominantly affecting the extracranial branches of the carotid arteries and the subclavian and axillary branches of the aorta. GCA may present with systemic symptoms such as fever, but the most common symptom is temporal and occipital headache accompanied by scalp tenderness. The arterial blockage associated with GCA leads to ischemic symptoms such as jaw claudication, intermittent claudication of the tongue and muscles involved in swallowing, and rarely infarction of the scalp or the tongue. GCA causes significant complications, particularly vision loss (4% for patients with large-vessel GCA and 11% for those with cranial disease). There are currently few real-world data available in France on the management of patients with GCA and on their treatment sequences. We propose to conduct an observational study aiming to describe GCA management and patient characteristics in France.
Study objectives	**Primary objective** The primary objective is to describe medical practices in patients with GCA in terms of patient journey, diagnostic methods and specific GCA treatments since diagnosis. **Secondary objectives** ➢ To describe comorbidities related to glucocorticoids (GCs) and associated treatments ➢ To describe GCA characteristics in terms of GCA duration, initial presentation, clinical form and GCA activity ➢ To describe the health status of GCA patients ➢ To describe physician and patient characteristics

Study methodology	Cross-sectional, non-interventional, national (France), multicentre study, conducted on a population of 300 patients with GCA, to describe GCA management and patient characteristics. The information will be collected during a single visit to the internist or rheumatologist as part of the usual management of the patient with GCA. The physician will not perform any additional examinations specific to the study. The physician will inform the patient about the study before inclusion and seek her/his non-opposition. A patient information form will be given to each patient by the physician. Patients who are eligible to take part in the study and who verbally agree to their data undergoing automated processing, will be included in the study. Data will be collected from the medical file and from patient questionnaires on health status (SF-36 [36-Item Short Form Survey Instrument], EQ5D [EuroQol-5 Dimensions]) and fatigue (FACIT-fatigue). In addition, GCA activity will be evaluated using a global arteritis activity Visual Analog Scale (VAS) to be completed by the patient and the physician (Figure 1). The study will be conducted in accordance with the professional code of ethics and the good epidemiological practice guidelines developed by the Association of French-Speaking Epidemiologists) (ADELF; 2017). **Figure 1 Study design** 

Number of physicians and method used to select them	A national data base provided by an independent company (CEGEDIM) including approximately 2600 internists and rheumatologists practicing in hospitals or private clinics in Metropolitan France will be used to recruit 150 active (i.e. inclusion of at least 1 patient) physicians for the study. Each physician will have a specific site number. Physician will be selected by the Sponsor following rules and recommendations on relations between industry and health professionals.
Number of patients and method used to select them	It is expected that 300 patients (incident cases, i.e. newly diagnosed or prevalent) will be recruited in this study. Based on a previous study on GCA patients (database analysis of the Echantillon Généraliste des Bénéficiaires), there are 2300 incident patients/year in France. Therefore, 300 incident and prevalent patients during the recruitment period seems realistic. Physicians will start patient inclusion only when the study is initiated at their site and when all regulatory authorisations are obtained. Each physician will be requested to include consecutively during the inclusion period, all the patients meeting the eligibility criteria listed below and accepting to participate in the study. In order to avoid any over-representation of a particular site or hospital, a maximum of 10 patients per hospital department will be able to participate in the study.
Patient selection criteria	**Inclusion criteria** Patients must meet the following criteria to be included in the study: ◗ At least 50 years old. ◗ Suffering from GCA as per investigator judgement, newly diagnosed or not. ◗ Starting or under treatment for GCA. ◗ Informed verbally and in writing about this study and not objecting to their data being electronically processed or subjected to data quality control. **Non-inclusion criteria** The patients fulfilling the following criteria cannot be included in the study: ◗ Unable to consent ◗ Participation to a randomised controlled clinical trial

Physician data collected	The following data will be collected from the physicians who have agreed to participate: physician location, gender, medical specialty, type of activity (public hospital, private hospital, both hospital and office-based, other), number of GCA diagnosis within the last previous year, year of medical school graduation, number of years of practice.
Patient data collected	The following information will be recorded in an electronic Case Report Form (eCRF) using the data available in the medical file or collected during the visit (as part of the routine patient management): ◗ Date of the inclusion visit (the only study visit) and type of visit (outpatient visit, day hospital, in-patient hospitalisation). ◗ Patient eligibility criteria. ◗ Demographic data: year of birth, gender, smoking status ◗ Clinical data: height, weight, medical history, comorbidities related to GCs ◗ GCA patient journey: Incident or prevalent patient (threshold: 6 weeks before visit), date of initial diagnosis, date of GCA signs/symptoms, physician(s) who referred the patient. ◗ GCA characteristics: Initial presentation (cranial, polymyalgia rheumatica, extracranial, ESR/CRP, general signs), diagnosis methods, clinical form (relapsing, GCs-dependence, with GCA complications), GCA activity (clinical signs and symptoms) ◗ Treatments: previous and on-going specific GCA treatments since diagnosis (GCs, immunosuppressants, targeted biologic therapy, Janus kinase inhibitors), treatments at diagnosis and inclusion visit, treatments for comorbidities related to GC intake. Four paper questionnaires (SF-36, EQ5D, FACIT-fatigue, global arteritis activity VAS) will be completed by the patient and one by the physician (global arteritis activity VAS). All questionnaires will be returned in the pre-paid reply envelope to the CRO in charge of the data entry. No safety data will be collected. Physicians will report adverse event as per usual French process, if appropriate. The use of indirectly personally identifiable data is crucial in this study since it will allow quality control. Physicians may be requested written corrections for missing or inconsistent data essential to the study. Patient identity will be coded in the eCRF and the questionnaires. The patients will be identified using a number made up of 4 digits: 3 digits for the investigator and 1 digit for the inclusion order number. The physician will maintain a patient identification table with patient's identity and corresponding study number. This table will be stored by the

	physician in a secure manner and no one else will have access to it. At the end of the study, the physician will be responsible for destroying this table.
Statistical analyses	**Study populations** 3 populations will be defined for the analyses: ➢ Population of Physicians: all the specialists who have included at least one patient fulfilling the inclusion criteria for the study ➢ Total Population: all included patients ➢ Analysis Population: included patients meeting the eligibility criteria **General statistical methods** The analyses of the primary and secondary objectives will be performed on the Analysis Population. The statistical analysis will be performed using SAS® software, version 9.3 or upper. The descriptive summary statistics will be for quantitative parameters: mean, standard deviation, median, first and third quartiles, minimum and maximum, filled and missing data. For qualitative parameters statistics will be frequency, percentage per modality, filled and missing data. As this is a descriptive study, no statistical testing will be performed. However, 2 sided 95% confidence intervals will be calculated for every relevant proportion / mean. **Primary objective analysis** In order to describe medical practices in patients with GCA, the following end points will be used on the analysis population: <u>Patient journey</u> ➢ Proportions of each physician who referred the patient ➢ Proportions of each physician who follows the patient for his/her GCA (internist/rheumatologist) ➢ Time between signs/symptoms and diagnosis: described as quantitative variable and as qualitative variable (early diagnosis / diagnosis in the standard time / late diagnosis).

<table>
<tr><td></td><td>
The 3 endpoints will be described overall and by subgroups: the first 2 endpoints will be described by time between signs/symptoms and diagnosis (qualitative variable) and the 1st and 3rd endpoints will be described by type of physicians who follows the patient.

<u>Diagnostic mean</u>

➢ Proportions of each diagnostic method used

The diagnostic mean will be described overall, by time between signs/symptoms and diagnosis (qualitative variable), and by type of physicians who follows the patient.

<u>Previous and on-going specific GCA treatments since diagnosis</u>

➢ Previous and on-going specific GCA treatments since diagnosis

Treatments will be coded using the WHO Drug medicine dictionary (ATC codes). They will be described overall and by type of physician who follows the patient.
</td></tr>
<tr><td>Planned Study duration and schedule</td><td>
The planned recruitment period of patients will be 5 months, from the 1st of June to the 31th of October 2018.

Study Milestones
<table>
<tr><th>Milestone</th><th>Planned Date</th></tr>
<tr><td>Study start date (start of enrolment and data collection)</td><td>01/06/2018</td></tr>
<tr><td>Study end date (end of enrolment and data collection)</td><td>31/10/2018</td></tr>
<tr><td>Interim analysis</td><td>NA</td></tr>
<tr><td>Final report of study results</td><td>Q2 2019</td></tr>
</table>
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CONTENT

LIST OF FIGURES

ABBREVIATIONS

CPF	CHUGAI PHARMA FRANCE
CRO	Contract Research Organization
EGB	Echantillon Généraliste des Bénéficiaires
EQ5D	EuroQol-5 Dimensions
EULAR	European League Against Rheumatism
GCs	GlucoCorticoids
GCA	Giant Cell Arteritis
LTD	Long-Term Disease
MTX	Methotrexate
PET	Positron Emission Tomography
PMR	PolyMyalgia Rheumatica
SAP	Statistical Analysis Plan
SF-36	36-Item Short Form Survey Instrument
TAB	Temporal Artery Biopsy
VAS	Visual Analog Scale

1 INTRODUCTION AND RATIONALE FOR THE STUDY

Giant cell arteritis (GCA) - also known as temporal arteritis, cranial arteritis, or Horton's disease - is a form of immune-mediated inflammatory systemic vasculitis that affects large and medium-sized arteries, predominantly affecting the extracranial branches of the carotid arteries and the subclavian and axillary branches of the aorta (Zöller et al. 2013). GCA may present with systemic symptoms such as fever, but the most common symptom is temporal and occipital headache accompanied by scalp tenderness (Babigumira et al. 2017). The arterial blockage associated with GCA leads to ischemic symptoms such as jaw claudication, intermittent claudication of the tongue and muscles involved in swallowing, and rarely infarction of the scalp or the tongue (Babigumira et al. 2017).

GCA causes significant complications, particularly vision loss (4% for patients with large-vessel GCA and 11% for those with cranial disease (Muratore et al. 2014). GCA patients are also 17.3 times (95% CI, 7.9 to 33.0) more likely to develop thoracic aortic aneurysm and 2.4 times (95% CI, 0.8 to 5.5) more likely to develop isolated abdominal aortic aneurysm (Evans, O'Fallon, et Hunder 1995).

The mainstay of GCA clinical management is initiation of high-dose glucocorticoids (GCs), typically prednisone from 0.7 to 1mg/kg/day (PNDS 2017) maintained and tapered gradually. In most patients, the administration of high-dose GCs is followed by a rapid improvement of systemic inflammatory signs, presumably due to the effective suppression of interleukin-6 and the acute-phase response. In current practice, the tapering of GCs is generally started once reversible clinical signs have abated and laboratory values have been normalized. The dose of prednisone is initially reduced by 10 to 20% every 2 weeks; once the dose falls below 10 mg per day, tapering is usually slowed (generally by 1 mg per month). These recommendations match those developed by the British Society for Rheumatology (BSR) (Dasgupta et al. 2010) and by the French study group for Large Vessel Vasculitis (GEFA) (Bienvenu et al. 2016a). Guidelines from the European League Against Rheumatism (EULAR) suggest a faster initial tapering to a dose of 10 to 15 mg per day within 3 months after treatment initiation (Mukhtyar et al. 2009).

It is well-known that GC treatment may cause various adverse effects. During a 10-year follow-up of a population-based cohort of patients with GCA, more than 80% had at least one complication related to GC treatment (Proven et al. 2003). The risk of cardiovascular comorbidities was over 6 times greater in GCA patients compared to matched controls (Pugnet et al. 2016).

Different steroid-sparing agents have been used, from antimalarial agents to immunosuppressants (Kötter et al. 2012) and targeted biologics therapies (Bienvenu et al. 2016b) with a more or less high level of evidence.

Recommendations from the EULAR include the use of methotrexate (MTX) as a potential adjunct to GCs in patients with large-vessel vasculitis (Mukhtyar et al. 2009), but supporting evidence is limited. A meta-analysis of three placebo-controlled randomized trials involving patients with newly diagnosed GCA showed that a regimen of GC therapy plus MTX as compared with GCs alone confers a significant but modest benefit in lowering the relapse rate and in reducing the cumulative dose of GCs, without reducing the side effects of the GCs (Mahr et al. 2007).

Among biologics, the interleukin-6 receptor antagonist tocilizumab has shown efficacy in the induction and maintenance of remission in patients with GCA in a phase III randomized double-blind, placebo-controlled trial combined with a 26-week prednisone taper (Stone, Klearman, et Collinson 2017). Tocilizumab has a marketing authorisation since September 18th, 2017 in Europe.

There are currently few real-world data available in France on the management of patients with GCA, on their treatment sequences, as well as on the costs related to their health care consumption.

To answer these questions, a first observational retrospective cohort study was conducted, using the EGB (Echantillon Généraliste des Bénéficiaires) database, which is a 1% random and representative sample of the French national Health insurance system.

EGB contains anonymous demographic and comprehensive medical data on conditions with long-term disease (LTD) status, hospitalizations, and reimbursement claims for medications dispensed in the community setting. The study used the data collected between January 1st, 2007 and December 31, 2015. Patients ≥50 years old, with a hospitalization for GCA and/or LTD status for GCA (M31.5 or M31.6 ICD-10 codes) and with at least 4 drug dispensing of oral GCs within 6 months around the index date were included.

The index date was defined as the date of first occurrence of GCA code and cases were considered being incident if the GCA code first occurred after a minimal follow-up of 2 years. A treatment sequence was defined as the start of a new drug or the resumption of the same drug after a stop of drug dispensing ≥ 3 months. Annual incidence rates were calculated for the period 2009 to 2015 by using the people recorded in the EGB database as denominator.

Briefly, the results were the following: among the 752,717 patients recorded in the EGB database, 241 people fulfilled inclusion criteria with a mean follow-up of 3.7 (±2.6) years. Annual incidence was ranging between 7 and 10/100,000 people ≥50 years-old that is 2300 patients/year. Demographic analyses showed that 72% of the patients were females and that mean age was 77.5 (±8.9) years. 74.3% of the patients had at least one proxy (i.e ICD-10 code or a treatment) for hypertension, 39.4% for depression/insomnia and 33.6% for osteoporosis. After index date, temporal artery biopsy (TAB) was performed in 43.2%, high-resolution color Doppler ultrasound in 35.3% and 18FDG-positron emission tomography (PET) in 11.6%.

Regarding treatments, 84.3% of the patients used only GCs while 16.7% also received 1 to 3 adjunctive medications, mainly MTX. Mean 1st GCs sequence duration was 17.2 months (±16.5) in 96.6% of the patients.

EGB database strengths included comprehensive patient demography, epidemiology, diagnostic methods and treatment sequences. In contrast, limited data were available for comorbidities (as only proxies were described), clinical presentations (cranial, polymyalgia rheumatica [PMR], extracranial), clinical forms (relapsing, GCs-dependant), doses of GCs used, cumulative GCs doses and GCs associated toxicities. In addition, patient journey was poorly described given that patients may be first seen by a variety of physicians according to their first signs and symptoms (e.g. ophthalmologist for blurred vision, neurologist for headache, etc.), data which was not available in the EGB database analysis.

The proportions of use of TAB, Ultrasound or PET have also to be confirmed as they thought to be unusually performed in the EGB analysis.

We propose to conduct an observational study aiming to describe GCA management and patient characteristics in France.

2 STUDY OBJECTIVES

2.1 Primary objective

The primary objective is to describe medical practices in patients with GCA in terms of patient journey, diagnostic methods and specific GCA treatments since diagnosis.

2.2 Secondary objectives

The secondary objectives of this study are:

- To describe comorbidities related to GCs and associated treatments
- To describe GCA characteristics in terms of GCA duration, initial presentation, clinical form and GCA activity
- To describe the health status of GCA patients
- To describe physician and patient characteristics

3 STUDY METHODOLOGY

3.1 General methodology

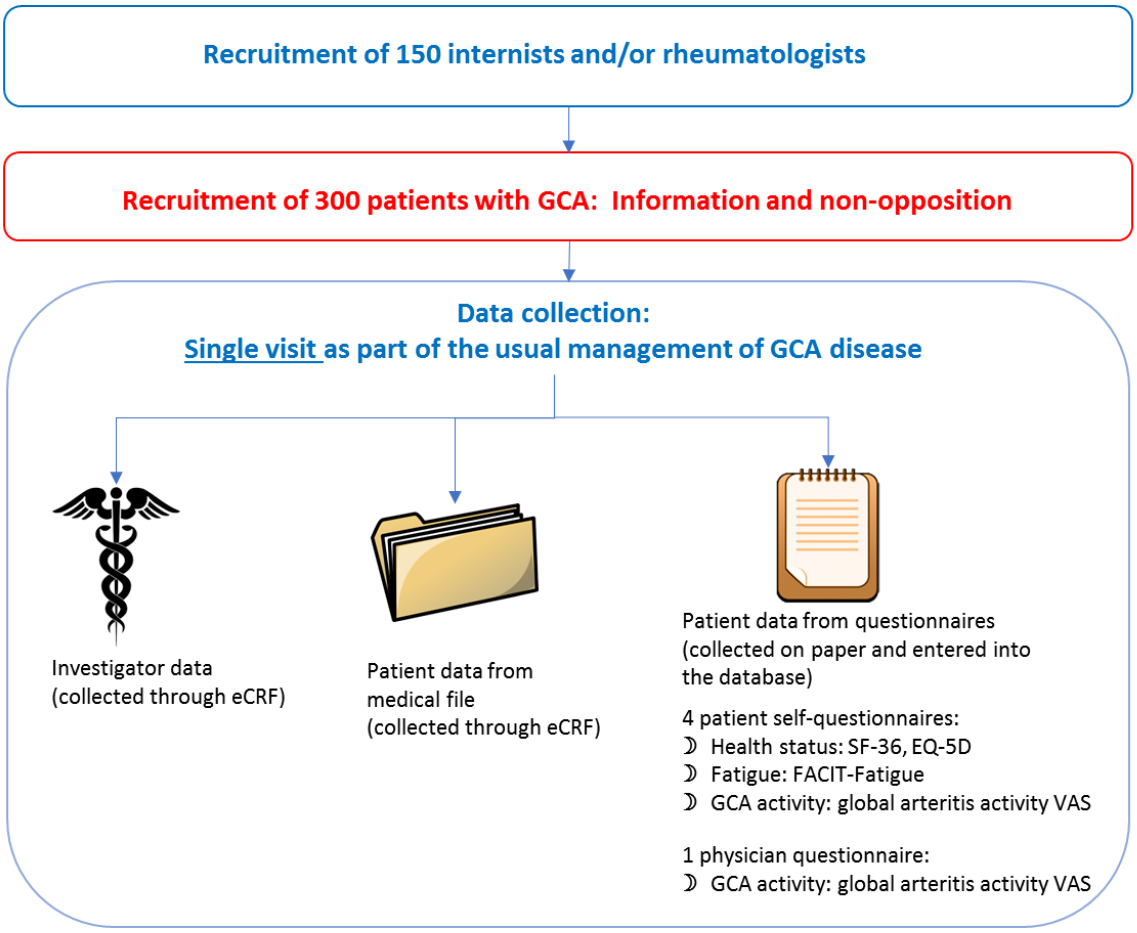
This is a cross-sectional, non-interventional, national (France), multicentre study, conducted on a population of 300 patients with GCA, to describe GCA management and patient characteristics (Figure 1).

The study will be conducted in accordance with the professional code of ethics and the good epidemiological practice guidelines developed by the Association of French-Speaking Epidemiologists)(ADELF; 2017) and the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) recommendations for the drafting of reports and publications related to the study (Vandenbroucke et al. 2007) (see also Section 12 for the full regulatory framework).

The information will be collected during a single visit to the internist or rheumatologist as part of the usual management of the patient with GCA. This study does not require any additional specific examination. Data will be collected from the medical file and from patient questionnaires on health status (SF-36 [36-Item Short Form Survey Instrument] McHorney, Ware, et Raczek 1993; Ware et Sherbourne 1992, EQ5D [EuroQol-5 Dimensions] Brooks 1996; EuroQol Group 1990; Rabin et al. 2014 and fatigue [FACIT-fatigue] Webster, Cella, et Yost 2003). In addition, GCA activity will be evaluated using a global arteritis activity Visual

Analog Scale (VAS) to be completed by the patient and the physician. These questionnaires are detailed in Section 5.3.2.

Figure 1 Study design



GCA: Giant Cell Arteritis; eCRF: electronic Case Report Form; VAS: Visual Analog Scale

3.2 Constitution and role of the Scientific Committee

A specialised Scientific Committee has been established to advise and support CHUGAI PHARMA FRANCE (CPF), to refine and validate the entire scientific project, including its scientific relevance and its objectives, modalities for selecting physicians and patients, the documents used for data collection, data quality control procedures during the study and the clinical interpretation of the statistical results.

In addition, the Scientific Committee will be consulted by CPF on any medical or scientific questions arising during the study as well as for validation of the statistical analysis plan, for the presentation of the final results to refine the analyses and to support a scientific communication plan of the results.

The four members of the Scientific Committee are:

- Prof Valerie Devauchelle-Pensec, Rheumatology Department, CHU LA CAVALE BLANCHE, BREST
- Prof Eric Hachulla, Internal Medicine Department, CHRU LILLE, LILLE
- Prof Alfred Mahr, Internal Medicine Department, HOPITAL SAINT LOUIS, PARIS
- Prof Marc Paccalin, Internal Medicine and Geriatic Medicine Department, CHU LA MILETRIE, POITIERS

3.3 Study duration and provisional schedule

The planned dates for the study milestones are provided in Table 1.

The planned period for recruiting patients will be 5 months, from the 1st of June to the 31th of October 2018.

Table 1 Study Milestones

Milestone	Planned Date
Study start date (start of enrolment and data collection)	01/06/2018
Study end date (end of enrolment and data collection)	31/10/2018
Interim analysis	NA
Final report of study results	Q2 2019

The overall duration of the study or the duration of the patient recruitment period may vary depending on the rate at which patients are included or the time it takes to obtain regulatory authorisations.

3.4 Physician recruitment and study initiation

3.4.1 Definition of the source file for physicians

The physician population in this study will include internists and rheumatologists who manage patients suffering from GCA in hospitals or private clinics in France and agree to take part in the study.

A national data base provided by an independent company (CEGEDIM) including approximately 2600 internists and rheumatologists practicing in hospitals or private clinics in Metropolitan France will be used to recruit 150 active physicians for the study.

Physician will be selected by the Sponsor following rules and recommendations on relations between industry and health professionals.

3.4.2 Methods of recruitment of the specialist physicians

A mailing including a reply coupon will be sent to all physicians mentioned in Section 3.4.1. This mailing will contain information about the study. A telephone follow-up phase is planned for physicians who have not responded to the mailing until the physician recruitment objective is met.

A Participation Agreement will be sent to each physician interested in participating in the study.

Once a site is initiated, the professional characteristics of the physician will be collected. The data will be used to perform a comparison with national data, in order to identify a potential selection bias (see also Section 9.1)

3.4.3 Recruitment hypotheses

The recruitment objective is 150 active physicians (i.e. will include at least one patient).

3.4.4 Initiation of the study

Following the signature of the study financial contract, physicians will be provided with all the study material (sent by post).

The participating physicians will then be trained on the study protocol and its practical aspects by telephone or online (video posted on a website) according to their preference.

If the physician chooses a study initiation by video, he/she will receive a login and password to access to a website where the initiation video will be uploaded.

During this telephone contact or video, all the key points necessary to the proper conduct of the study will be addressed: the rationale and objectives of the study, regulatory requirements (patient information form, etc.), and also the technical requirements (data collection, shipment of the questionnaires, etc.). If the study is initiated by a telephone call, the minutes of the discussion and a presentation will be sent to the physician. In case of a study initiation by video, a quiz will be submitted to the physician to ensure that the training has been understood.

3.5 Patient selection

3.5.1 Patient selection method

Physicians will start patient inclusion only when the study is initiated at their site and when all regulatory authorisations are obtained.

It is expected that 300 patients (prevalent or incident cases) will be recruited in this study. Based on the previous EGB database analysis, there are 2300 incident patients/year in France. Thus, including 300 incident and prevalent patients during the recruitment period, even excluding summer holidays, seems realistic (see also Section 7.1).

Each physician will be requested to include consecutively during the inclusion period all the patients meeting the eligibility criteria listed below and accepting to participate in the study.

3.5.2 Information and consent

The physician must inform the patient about the study before inclusion and seek her/his non-opposition. A patient information form will be given to each patient by the physician. It will explain the purpose of collecting and processing the data, the nature of data collected, the persons who will receive the data, the patient's right to access and correct the data and also the patient's right to object to transmission of the data (as specified by the CNIL). The original will be kept by the investigator and a copy will be given to the patient.

Patients who are eligible to take part in the study and who verbally agree to their data undergoing automated processing (as defined by CNIL), will be included in the study by the physicians, who will enter the corresponding data in the eCRF. The patient agreement will be only verbal and will NOT include the collection of a non-opposition form.

Patient decision to participate or not in the study will be written in his/her medical file by the physician.

4 STUDY POPULATIONS

4.1 Physician population

In total, 150 internists and rheumatologists practicing in hospitals or private clinics in Metropolitan France are expected to participate actively in the study (i.e. inclusion of at least 1 patient) (see also Section 3.4 for the physician recruitment method).

In order to avoid any over-representation of a particular site or hospital, a maximum of 10 patients per hospital department will be able to participate in the study. Each physician will have a specific site number.

4.2 Patient population

A total of 300 patients meeting the selection criteria listed below will be included in the study.

4.2.1 Inclusion criteria

Patients must meet the following criteria to be included in the study:

- At least 50 years old.
- Suffering from GCA as per investigator judgement, newly diagnosed or not.
- Starting or under treatment for GCA.

- Informed verbally and in writing about this study and not objecting to their data being electronically processed or subjected to data quality control.

4.2.2 Non-inclusion criteria

Patients fulfilling the following criteria cannot be included in the study:

- Unable to consent
- Participation to a randomised controlled clinical trial

4.2.3 Withdrawal from the study

In this cross-sectional study, no specific criteria are defined for withdrawal from the study. The patient can refuse at any time that his/her data are analysed.

5 CONDUCT OF THE STUDY AND DATA TO BE COLLECTED

5.1 Conduct of the study

5.1.1 Inclusion consultation (single study visit)

Once the study initiation has been completed, patients will be included consecutively after verification that they meet the selection criteria (see section 4.2).

The information will be collected during a single visit to the internists and rheumatologist as part of the usual patient management of his/her GCA. The physician will explain the purpose of the study to the patient with an information form specific to the study and will inform him/her of the option to refuse or withdraw from participation. A copy of the information form will be given to the patient and the original will be kept by the physician.

The physician will perform this visit as part of the usual patient management and will not perform any additional examinations specific to the study.

The data collected from the medical file will be recorded on an electronic case report form (eCRF). Self-assessment questionnaires about health status (SF-36, EQ-5D), GCA activity (global arteritis activity VAS) and fatigue (FACIT-fatigue) (see also Section 5.3.2) will be proposed to the patient. He/she will have to complete them during the course of the visit. The physician will also complete a copy of the global arteritis activity VAS on paper. All questionnaires will be returned in the pre-paid reply envelope to the CRO ITEC Services, in charge of the data entry.

5.2 Physician Data collected

The following data will be collected from the physicians who have agreed to participate:

- Physician location

- Gender
- Medical specialty
- Type of activity: public hospital, private hospital, both hospital and office-based, other
- Number of GCA diagnosis within the last previous year
- Year of medical school graduation
- Number of years of practice

The analyses of this data will allow to identify any physician recruitment bias (see also Section 9.1.2).

The information will be recorded by the physician in the eCRF.

5.3 Patient Data collected

Patient identity will be coded in the eCRF and the self-assessment questionnaires. Patients will be identified using a number made up of 4 digits: 3 digits for the investigator and 1 digits for the inclusion order number (see also Section 12.5 on data confidentiality).

5.3.1 Case report form

No information related to patient identity (initials, full date of birth, etc) will be entered in the eCRF.

The following information will be recorded in the eCRF using the data available in the medical file or collected during the visit (as part of the routine patient management):

- Date of the inclusion visit (the only study visit) and type of visit (outpatient visit, day hospital, in-patient hospitalisation).
- Patient eligibility criteria.
- Demographic data:
    - Year of birth, gender,
    - Smoking status (smoker, never smoker),
- Clinical data:
    - Height, weight (at diagnosis, at the inclusion visit)
    - Medical history:
        - significant past and current comorbidities (e.g. diabetes, high blood pressure, dyslipidaemia, osteoporosis, neuropsychiatric disorders,

depression, insomnia, serious infection disease, parasitic diseases, cancer, stroke, coronary artery disease, ischemic cardiopathy, peripheral artery diseases, adrenal insufficiency, cataract, glaucoma, gastro-intestinal ulcer, digestive perforation, other significant history),

- start and stop date (month, year) of comorbidities

- Comorbidities related to GCs for GCA patients (i.e. which appeared or worsened during GCs treatment according to the investigator judgement).

- GCA patient journey:

  - Incident or prevalent patient:

    - Newly diagnosed (i.e. incident) patient will be defined as patient with GCA diagnosis within the last 6 weeks before visit

    - Not newly diagnosed (i.e. prevalent) patients will be defined as patient with GCA diagnosis more than 6 weeks before visit

  - Date of initial diagnosis

  - Date of GCA signs/symptoms (month and year)

  - Physician(s) who referred the patient (General Practitioner, Ophthalmologists, Neurologist, Emergency, Internist, Rheumatologist, Other).

- GCA characteristics:

  - Initial presentation at diagnosis and inclusion visit:

    - Cranial (localized headache, scalp tenderness, temporal artery tenderness or decreased pulsation, ischemia-related vision impairment / loss, mouth or jaw pain upon mastication, stroke or transient ischaemic attack (TIA), other)

    - PMR (morning stiffness and/or pain in the shoulder and/or pelvic girdles, inflammatory arthromyalgia, peripheral arthritis, other)

    - Extracranial (large-vessel GCA i.e. thoracic or abdominal aortic aneurysm, myocardial infraction, dilatation, limb claudication, subclavian stenosis, other)

    - ESR/CRP

    - General signs: fever, weight loss (%), health status modification

    Start date for all signs and symptoms (month, year)

  - Diagnostic methods: TAB, High-resolution color Doppler ultrasound of the temporal arteries, MRI of the temporal arteries, 18FDG-PET, Computed tomography

angiography (CTA), Magnetic resonance angiography, signs/symptoms, erythrocyte Sedimentation Rate (ESR), C-Reactive protein (CRP), other.

- Clinical form:
  - Relapses: date (month, year), treatments and doses, criteria for identifying relapse (clinical, biological, other)
  - GCs-dependence: dose of prednisone after GCA diagnosis
  - Complications during the course of the disease: ischemia-related vision loss, stroke, TIA, thoracic or abdominal aortic aneurysm, other.

- GCA activity:
  - Clinical signs and symptoms of GCA activity at diagnosis and at inclusion: GCA-related fever (> 38°C), symptoms of PMR (morning stiffness and/or pain in the shoulder and/or pelvic girdles, inflammatory arthromyalgia, peripheral arthritis, other), localised headache, temporal artery or scalp tenderness, visual signs or symptoms (e.g. acute or subacute vision loss due to arteritic anterior ischemic optic neuropathy; A-AION), transient blurry vision (generally monocular or at least affecting one eye at a time, but potentially affecting both eyes), jaw or mouth pain, extremity claudication, other features judged by the investigator to be consistent with a GCA or PMR flare.

    Start date of signs and symptoms (month, year)

- Treatments:
  - Previous and on-going specific GCA treatments since diagnosis:
    - GCs (start and end date, dose/day, administration route, current dose, cumulative dose, kinetic)
    - Immunosuppressants (MTX, cyclophosphamide, cyclosporine, azathioprine, mycophenolate mofetil, leflunomide, dapsone, hydroxychloroquine, other) (start and end date, dose at starting date, current dose, maximum dose)
    - Targeted biologic therapy (adalimumab, etanercept, abatacept, tocilizumab, infliximab, other) (start and end date, dose at starting date, current dose)
    - Janus Kinase inhibitors (start and end date, dose at starting date, current dose)
  - Treatments at diagnosis and inclusion visit: antiplatelet agents, statins, antiosteoporotic treatments, antihypertensive (start date, treatment name).
  - Other significant concomitant treatments (start and end date, indication)

- Treatments for comorbidities related to GC intake (start and end date, indication)

No safety data will be collected. Physicians will report adverse event as per usual French process, if appropriate.

5.3.2 Questionnaires

Four paper questionnaires will be completed by the patient and one will be completed by the physician. All questionnaires will be returned in the pre-paid reply envelope to the CRO ITEC Services, in charge of the data entry.

5.3.2.1 Self-assessment patient questionnaires:

- SF-36 (McHorney, Ware, et Raczek 1993; Ware et Sherbourne 1992): The SF-36 questionnaire is a generic health status instrument evaluating 8 dimensions through 36 questions: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions. An additional item provides an indication of perceived change in health (Annexe 15.1).

- EQ5D-3L (Brooks 1996; EuroQol Group 1990; Rabin et al. 2014): The EQ-5D questionnaire is a generic health status instrument composed of 5 questions and a VAS. The questions explore 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems, extreme problems. The visual analogue scale evaluates the perceived health state (Annexe 15.2).

- FACIT-fatigue (Webster, Cella, et Yost 2003): FACIT-Fatigue is an instrument that measures overall fatigue and its effects on the general functioning and daily activities through 13 questions. Completion of the questionnaire should be based on a 7-day recall period. Each question has 5 levels: not at all, a little bit, somewhat, quite a bit, very much. Lower scores indicate greater fatigue (Annexe 15.3).

- Patient global arteritis activity VAS: This VAS measures global arteritis activity on a scale of 100 mm labelled with “no disease activity” (symptom-free and no arteritis symptoms) at the extreme left and with “maximum disease activity” (maximum arteritis disease activity) at the extreme right. The patient will be asked to indicate his/her disease activity by drawing a line on the scale (Annexe 15.4).

5.3.2.2 Physician questionnaire:

- Physician global arteritis activity VAS: This VAS measures global arteritis activity, as described above. The physician will be asked to indicate the patient disease activity by drawing a line on the scale.

6 ENDPOINTS

6.1 Primary endpoints

The endpoints of the primary objective *To describe medical practices in patients with GCA in terms of patient journey, diagnostic methods and specific GCA treatments since diagnosis* are:

- Patient journey (Proportions of each physicians who referred the patient, Proportions of each physicians who followed the patient for his/her GCA, Time between GCA signs/symptoms and diagnosis)
- Proportions of each diagnostic method used
- Previous and on-going specific GCA treatments since diagnosis

6.2 Secondary endpoints

The endpoints of the objective *To describe comorbidities related to GCs and associated treatments* are:

- Comorbidities related to GCs
- Treatments in patients with comorbidities related to GCs

The endpoints of the objective *To describe GCA characteristics in terms of GCA duration, initial presentation, clinical form and GCA activity*:

- Proportion of incident patients: patients with a diagnosis of GCA ≤ 6 weeks from inclusion
- Proportion of prevalent patients: patients with a diagnosis of GCA > 6 weeks from inclusion.
- GCA duration
- Initial presentation: Proportions of patients with cranial GCA, PMR, extracranial GCA, elevated ESR/CRP and general signs.
- Clinical form: Proportion of patient with relapse and number of relapse, Distribution of GCs-dependence, Proportions of patients with GCA complications
- Proportions of each clinical signs/symptoms of GCA activity
- Score of the physician and patient global arteritis activity VAS

The endpoints of the objective *To describe the health status of GCA patients* are:

- PRO scores: Total and detailed scores of the SF-36 questionnaire, detailed scores of the EQ5D-3L questionnaire, Total and detailed scores of the FACIT-Fatigue questionnaire

The endpoints of the objective *To describe physician and patient characteristics* are:

- Demography, medical specialty, number of years of practice, type of practice and number of GCA diagnosis within the previous year for physicians,
- Demography for patients
- Significant past and current comorbidities of GCA patients and associated concomitant treatments

7 STATISTICAL METHODS

7.1 Rationale for the number of patients and physicians

7.1.1 Number of patients required

Not applicable in a descriptive observational study

7.1.2 Number of physicians

Not applicable

7.2 Statistical analyses

The analysis will be performed by ITEC Services in accordance with this section and with the Statistical Analysis Plan (SAP) that supplements it.

7.2.1 General statistical methods

The statistical analysis will be performed using SAS® software, version 9.3 or upper.

A SAP describing the planned statistical analysis in detail with Tables, Figures and Listings (TFLs) templates will be developed as a separate document. This SAP will be finalised and validated before each database freeze by CPF.

The descriptive summary statistics will be:

- for quantitative parameters: mean, standard deviation, median, first and third quartiles, minimum and maximum, filled and missing data;
- for qualitative parameters: frequency, percentage per modality, filled and missing data

As this is a descriptive study, no statistical testing will be performed. However, 2 sided 95% confidence intervals will be calculated for every relevant proportion / mean.

7.2.2 Study populations

Three populations will be defined for the analyses:

- Population of Physicians: all the specialists who have included at least one patient meeting the eligibility criteria for the study

- Total Population: all included patients

- Analysis Population: all included patients meeting the inclusion and non-inclusion criteria

The number of potential exclusions from the patient population used for analysis and the reasons for these exclusions will be described. The patient disposition will be described.

7.2.3 Analysis of the physician and patient populations

The analyses of the primary and secondary objectives will be performed on the Analysis Population.

7.2.3.1 Analyses of primary objectives:

To describe medical practices in patients with GCA, the following endpoints will be described on the analysis population:

Patient journey

- Proportions of each physician who referred the patient

- Proportions of each physician who follows the patient for his/her GCA (internist/rheumatologist)

- Time between signs/symptoms and diagnosis: described as quantitative variable and as qualitative variable. (early diagnosis / diagnosis in the standard time / late diagnosis)

The 3 endpoints will be described overall and by subgroups: the first 2 endpoints will be described by time between signs/symptoms and diagnosis (qualitative variable) and the 1st and 3rd endpoints will be described by type of physicians who follows the patient.

Diagnostic mean

- Proportions of each diagnostic method used

The diagnostic mean will be described overall, by time between signs/symptoms and diagnosis (qualitative variable), and by type of physicians who follows the patient.

Previous and on-going specific GCA treatments since diagnosis

- Previous and on-going specific GCA treatments since diagnosis

Treatments will be coded using the WHO Drug medicine dictionary (ATC codes). They will be described overall and by type of physician who follows the patient.

7.2.3.2 Analyses of secondary objectives

The analysis of the secondary objectives will be performed on the analysis population.

Description of comorbidities related to GCs and associated treatments

- Current and past comorbidities of GCA patients (comorbidities related to GCs) will be coded using the medical dictionary MedDRA®. They will be described overall and by type of physicians who follows the patient.
- Treatments in patients with comorbidities related to GCs will be coded using the WHO Drug medicine dictionary (ATC codes). They will be described overall and by type of physician who follows the patient.

Description of GCA characteristics

- Time between diagnosis and inclusion will be described as quantitative variable and as qualitative variable (patient newly diagnosed or not: incident or prevalent case)
- Proportion of incident patients: patients with a diagnosis of GCA ≤ 6 weeks from inclusion
- Proportion of prevalent patients: patients with a diagnosis of GCA > 6 weeks from inclusion.

The following endpoints will be described overall and by type of patient (prevalent/incident), by time between signs/symptoms and diagnosis (qualitative variable), and by type of physicians who follows the patient:

- GCA duration
- Initial presentation: proportions of patients with cranial GCA, PMR, extracranial GCA, ESR/CRP, general signs
- Clinical form
    - Proportion of patients with relapse and number of relapse,
    - Proportion of patients with recurrence and number of recurrences,
    - Dose of GCs-dependence
    - Proportion of patients with GCA complications.

Analysis of potential factors associated to relapse will be performed using logistic regression. The associated factors will be defined in the SAP.

- GCA activity
    - Proportions of each clinical signs/symptoms of GCA activity

- Scores of the patient and physician global arteritis activity VAS (quantitative variable)

The concordance between the scores of the patient and physician global arteritis activity VAS will be evaluated using the kappa coefficient.

The potential factors associated with the increase of the global arteritis activity will be studied.

Description of the health status of GCA patients

- SF-36 questionnaire

The SF-36 is a self-report, 36 item survey measuring health-related quality-of-life. The SF-36 consists of eight scaled scores. A score ranging from 0 (indicating the worse health status) to 100 (indicating the best health status) is assigned for each domain. Scores and missing data of the SF-36 were handled according to the user's manual. The score for each item of SF-36 will be presented (in quantitative) as well as the total score for each domain.

- EQ5D-3L questionnaire

The EQ5D-3L consists of five questions relating to five dimensions of health. Respondents indicate which of a possible three statements best describe their current health state for each dimension. Each dimension has 3 levels: no problems, some problems, extreme problems. Respondents are asked to repeat this process for the five dimensions by indicating one level for each dimension, giving rise to scores ranging from 1 to 3, with scores of 3 on each dimension indicating the most severe impairment. Binary variables will be computed for each dimension dichotomising the levels into 'No problems' (level 1) and 'Problems' (levels 2 and 3). Perceived current health state will be measured by asking respondents to indicate their current health state on a VAS with endpoints labelled 0 'Worst imaginable health state' and 100 'Best imaginable health state. The score for each item of EQ5D-3L will be presented (in qualitative variable at 2 and 3 modalities for 5 dimensions and in quantitative for VAS).

- FACIT-Fatigue

FACIT-Fatigue is a patient-reported rating scale consisting of 13 items that yields a summed total score ranging between 0 and 52 (52= less fatigue).

The score for each items of FACIT-Fatigue will be presented (in qualitative variable) as well as the total score (quantitative variable).

Description of physician and patient characteristics

- Description of physicians

The analysed data will be recorded by the physician in the eCRF.

The population of physicians in the study will be described overall, in terms of demographic parameters (geographic location, number of years of practice, year of medical school graduation), medical specialty, status of the health institution (public hospital, private hospital, both hospital and office-based, other) and number of GCA diagnosis within the previous year.

- Description of patients

Demographic data (age, gender, smoking status) and body mass index will be described overall and by type of physician who follows the patient.

Current and past comorbidities of GCA patients (significant past and concomitant diseases) will be coded by the medical dictionary MedDRA®. They will be described overall and by type of physician who follows the patient.

Treatments will be coded using the WHO Drug medicine dictionary (ATC codes). They will be described overall and by type of physician who follows the patient.

7.2.4 Schedule for data analysis

The final analyses will be performed after the database lock and are planned for January 2019.

8 DATA MONITORING AND CONTROL

8.1 Centralised monitoring and controls

Monitoring of the study will be performed by ITEC Services, which will ensure, through regular communication (follow-up telephone calls and/or sending out newsletters) that the study is being conducted in accordance with the protocol and the regulatory requirements.

Monitoring visits will be conducted in 10% of active sites. The objective of these visits will be to validate the existence of the patients included in the study, and to check that the data reported in the CRF are consistent with the available source data. Monitoring visits will be described in the study monitoring guide and a monitoring report will be prepared after each visit.

The first questionnaires from each site will be monitored upon reception to ensure that the completion method is correct and that a follow up training is not necessary.

A specific Freephone number will be available for physicians having any questions related to the study.

Requests for corrections will be sent by Data Management for missing or erroneous CRF data on a regular basis, according to the Data Management Plan of the study. They will be transmitted to the Epidemiology Research Associate, who will manage the resolution with the physician through the eCRF, followed by emails and phone calls if necessary.

The monitoring procedures will be validated by CPF.

In addition, a Data Review Meeting will take place prior to the final statistical analysis. Decisions made during this meeting will be validated by the study Scientific Committee.

8.2 Audit and on-site inspections

Prior to the start of the study, the investigator is required to confirm his/her agreement to conduct the study in accordance with the protocol and to give access to all relevant data and records to CPF monitors, auditors, and designated agents of CPF, IRBs/IECs, and regulatory authorities as required.

If an inspection of the site is requested by a regulatory authority, the investigator must inform CPF immediately that this request has been made.

9 LIMITATIONS OF THE STUDY

In order to extrapolate study results to the entire population, potential bias must be detected a priori and controlled as much as possible.

In this cross-sectional study, the description of patient management can be subject to selection bias during the recruitment of the study population (if the source population is not representative of the target population; if the active physician and included patient samples are not representative of the source population) (see also Section 7.1).

9.1 Bias in selection of the physicians and the patients during recruitment

9.1.1 Pre-inclusion controls

9.1.1.1 Selection of physicians

The physician selection method described in Section 3.4 should ensure the sample is representative.

9.1.1.2 Patient selection

The patients included should be selected in a consecutive manner by the participating physicians once the study has been initiated and the selection criteria have been verified. In order to encourage inclusions in a consecutive manner, this obligation will be highlighted:

- in the financial contract signed by the physician,
- during regular follow-up contacts with the physicians during the recruitment period (telephone calls and/or Newsletters).

9.1.2 Post-inclusion controls

At the end of the inclusion period, the characteristics of the physicians who are active in the study will be compared to those of the physicians in the source list, on the basis of the available

data. Any significant differences in these parameters will be discussed with the members of the study Scientific Committee.

The distribution of included patients will be compared to the distribution of the specialists who are active in the study (geographic distribution and distribution by clinical practice facility).

In addition, the patient and GCA characteristics at baseline will be discussed with the study Scientific Committee and compared to the data available in the literature at this time.

10 REPORTING OF ADVERSE REACTIONS

This is a non-interventional epidemiological study. It does not aim to identify or quantify any safety risk related to an authorised medicine. Therefore, no safety data will be collected and no reporting of adverse reactions is expected in this study.

Physicians will report adverse event as per usual French process, if appropriate.

11 STUDY DISCONTINUATION

Planned study duration is 4 months (recruitment period and data collection). Given the cross-sectional nature of the study, no study discontinuation is expected. If the patient withdraws her/his consent after the unique visit, all data generated until study discontinuation and the reasons for not completing the study will be collected.

12 ETHICAL AND LEGAL CONSIDERATIONS

12.1 Regulatory framework of the study

This non-interventional study is conducted in accordance with Article L. 1121-1 of the French Code of Public Health defining non-interventional studies as "all the acts are practised and products used in the usual way, with no risk and constraint for the patient".

This study does not result in any changes to the patient’s usual medical care, does not cause physical or psychological harm and does not require particular follow-up visits for subjects entering the study. The use of study drug is consistent with the marketing authorisation as referred to Article L.5121-8 of the French Code of Public Health (CSP).

In this context, the study is not subject to the regulations applicable to interventional research.

Competent Authority (French National Agency for Medicines and Health Products Safety - ANSM) authorisation is not required but a positive opinion from the French Ethics Committee will be mandatory before the start of the study.

The study will comply with the MR003 methodology reference, in which case there is no specific regulatory procedures (check of the MR 003 applicability should be documented).

The study has been designed and shall be implemented in accordance with applicable regulation, including:

- The French Code of Public Health (pharmacovigilance, the anti-gift law, transparency, Jardé law, etc),
- regulations on the protection of personal data,
- the Declaration of Helsinki,
- "The ENCePP Code of Conduct for Scientific Independence and Transparency in the Conduct of Pharmacoepidemiological and Pharmacovigilance Studies, ENCePP, Rev.3 editorial amendment 14 July 2016,
- "Guide on Methodological Standards in Pharmacoepidemiology", European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP), EMA/95098/2010, Rev. 6 July 2017,
- "Guideline on good Pharmacovigilance practices: Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2) ", EMA, HMA, Rev.2 28 July 2017,
- "Good Epidemiological Practice (GEP)", International Epidemiological Association (IEA), November 2007
- "Guidelines for Good Pharmacoepidemiology Practices (GPP)", International Society for Pharmacoepidemiology (ISPE), June 2015
- "STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines" (Vandenbroucke, et al 2008)
- the Recommendations of Ethics and Good Practices in Epidemiology (French version - 2007), ADELF, ADEREST, AEEMA, EPITER.

12.2 Responsibility and insurance by CHUGAI PHARMA FRANCE

In France, since this study does not fall within the framework of biomedical research, no insurance is required.

12.3 Submission of the study contracts and protocol

Before the start of the study, the study protocol, the patient information form and all the other relevant documents will be submitted to the competent authorities in accordance with applicable legislation. All ethical and legal obligations must be met before the first patient is included in the study.

12.3.1 Ethics Committee

Pursuant to Law No. 2012-300 of March 5, 2012 on research involving humans (known as "Loi Jardé"), the study will be submitted to an Ethics Committee.

12.3.2 Protection of personal data

In accordance with Article 54 of Act No 78-17 of January 6, 1978 as amended, the processing of personal data for this non-interventional study is in accordance with Decision No 2016-263 of July 21, 2016 on the approval of a reference methodology for the processing of personal data used in medical research (MR-003), published in the OJ on August 14, 2016. CPF has signed a commitment to be compliant with reference methodology MR003 (02.03.2018 / n°: 2158700 v 0).

12.3.3 Submission of financial agreements to Medical Council

According to the Act on various social measures (DMOS - amended by the law of March 4, 2002), Article L. 4113-6 of the French Code of Public Health (CSP) prohibits companies "benefiting, producing or marketing products covered by compulsory social security schemes" from offering or providing direct or indirect benefits to healthcare professionals or associations representing or defend the interests of them. Article L. 4113-6 of the French Code of Public Health allows exemption if:

- an agreement with the healthcare professionals exists,
- the purpose of this agreement relates to research activities,
- this agreement is submitted for approval to the competent National Medical Council, which evaluate adequacy of the fees.

Therefore, the site agreements will be submitted to the French National Council of Physicians to seek a positive opinion.

12.3.4 Sunshine act

In accordance with Article L. 1453-1 of the French Code of Public Health (Article 2 of Law No 2011-2012 of 29 December 2011 on the Strengthening of Health Protection for Medicinal and Health Products) and Decree no. ° 2013-414 of May 21, 2013, CPF will disclose any agreements with healthcare professionals and healthcare institutions; as well as any transfers of values on the Ministry of Health dedicated website: https://www.entreprises-transparence.sante.gouv.fr.

12.4 Protocol amendment(s)

Neither the physician nor CPF is permitted to amend the study protocol without obtaining the written agreement of the other party. Once the study has started, amendments should only be made in exceptional circumstances. The amendments then become an integral part of the study protocol.

In accordance with local laws, the competent authorities will be informed of any subsequent amendment to the protocol.

Any significant change relating to the protocol will be the subject of a written report, including a description of the reasons for this change, particularly those made in relation to the quality of the study or at the request of the Sponsor or study Scientific Committee.

The amendments made to the study protocol will be submitted for an opinion to the French Ethics Committee.

12.5 Information for patients and confidentiality of the collected data

Before entering the study, the physician must inform the patient, using a vocabulary that the patient can understand, of the nature and objective(s) of the study and of the right to object to, access and correct his/her data. The physician will give the patient an information form.

The physician must ensure that the confidentiality of the patient data is strictly maintained and that their identity is protected from unauthorised parties.

The patient data collected in the eCRF and the paper questionnaires will be registered in coded form. The patients will be identified using a number made up of 4 digits: 3 digits for the investigator and 1 digits for the inclusion order number. The physician will maintain a patient identification table with patient’s identity and corresponding study number. The physician will be bound by professional secrecy and no one else will have access to it. This table will be stored by the physician in a secure manner. At the end of the study, the physician will be responsible for destroying this table. Names of patients will never be sent to the sponsor.

The physician must keep study documents in a safe location.

It must be possible to find all the information completed in the eCRF in the source data, stored in the patient's medical file.

12.6 Rationale for the use of personal data

The use of indirectly personally identifiable data is crucial in this study since it will allow quality control. Physicians may be requested written corrections for missing or inconsistent data essential to the study.

12.7 Financial agreement with the physicians

The physician and ITEC Services (appointed by CPF) will sign a specific financial agreement prior to the study, detailing all the responsibilities incumbent upon CPF and the physician, in

relation to the study. Compensation will be provided for each patient included; the terms and conditions of payment will be specified in the financial agreement.

12.8 Delegation of duties by the physician

The physician must ensure that all persons collaborating in the study have all the necessary information concerning the protocol, any potential amendments, as well as their duties and functions in the study.

12.9 Archiving

The key documents, as listed below, must be stored by the physician in a secure location that allows quick access if necessary. By signing the protocol, the investigator agrees to store these for a period of 5 years. However, a longer period could possibly be imposed by new regulatory requirements.

Key documents include, in particular:

- all the source documents,
- patient information form
- the patient identification list (i.e. the list of codes linking each patient number to the patient's identity).

The complete list of essential documents to be stored by the investigator for the purposes of the study will be provided by ITEC Services during the study set-up.

After the end of the study and at the end of the planned storage period, the physician has the responsibility to destroy the study documents (including the patient information forms and the patient identification list) and to inform the sponsor of this destruction.

Originals of all the study documents will be stored by CPF, except the patient identification list and the originals of the information forms which should never be sent to CPF or ITEC Services.

13 DOCUMENTATION AND USE OF THE STUDY RESULTS

13.1 Documentation of the study results

13.1.1 Documents completed by the physician

ITEC Services, appointed by CPF, will provide each physician, in a timely manner, with a sufficient quantity of all the documents needed to collect the study data.

The physician will enter into the eCRF all data collected from medical files as part of the protocol. The method for completing and correcting the eCRFs will be explained to the physician during the study initiation.

The physician must complete the eCRF as soon as possible after collecting the information, and preferably on the day of the visit.

The physician will also complete a questionnaire as described in Section 5.3.2.

13.1.2 Documents completed by the patient

After having been informed of the study by the physician, and if he/she agrees to participate, the patient will be asked to complete the 4 self-assessment questionnaires described in Section 5.3.2.

13.1.3 Study report

ITEC Services will produce a final study report in collaboration with CPF. The complete report (statistical and clinical) will be validated by the lead physician for the project at CPF and by the study Scientific Committee.

13.2 Use of the study results

All the information related to the operations of CPF and as yet unpublished scientific data provided by CPF is confidential and remains the sole property of CPF. The physician undertakes to use this information solely for the conduct of the study and not for any other reason, except with prior written agreement of CPF.

Any publication of the study results should comply with the publication rules of CPF.

The results of the study may be published or communicated orally during scientific conferences by members of the Scientific Committee after prior agreement has been obtained from CPF and the learned societies or cooperative groups that may be involved (scientific partnership).

In accordance with article L1122-1 of the Public Health Code in France, the patients may ask to be informed of the study results by his/her physician.

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15 APPENDICES

15.1 Appendix 1: 36-Item Short Form Survey Instrument (SF-36)

RAND 36-Item Health Survey 1.0 Questionnaire Items

Choose one option for each questionnaire item.

1. In general, would you say your health is:

- 1 - Excellent
- 2 - Very good
- 3 - Good
- 4 - Fair
- 5 - Poor

2. **Compared to one year ago**, how would you rate your health in general **now**?

- 1 - Much better now than one year ago
- 2 - Somewhat better now than one year ago
- 3 - About the same
- 4 - Somewhat worse now than one year ago
- 5 - Much worse now than one year ago

The following items are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
3. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	○ 1	○ 2	○ 3
4. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	○ 1	○ 2	○ 3
5. Lifting or carrying groceries	○ 1	○ 2	○ 3
6. Climbing **several** flights of stairs	○ 1	○ 2	○ 3
7. Climbing **one** flight of stairs	○ 1	○ 2	○ 3
8. Bending, kneeling, or stooping	○ 1	○ 2	○ 3
9. Walking **more than a mile**	○ 1	○ 2	○ 3
10. Walking **several blocks**	○ 1	○ 2	○ 3
11. Walking **one block**	○ 1	○ 2	○ 3
12. Bathing or dressing yourself	○ 1	○ 2	○ 3

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?

	Yes	No
13. Cut down the **amount of time** you spent on work or other activities	○ 1	○ 2
14. **Accomplished less** than you would like	○ 1	○ 2
15. Were limited in the **kind** of work or other activities	○ 1	○ 2
16. Had **difficulty** performing the work or other activities (for example, it took extra effort)	○ 1	○ 2

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

	Yes	No
17. Cut down the **amount of time** you spent on work or other activities	○ 1	○ 2
18. **Accomplished less** than you would like	○ 1	○ 2
19. Didn't do work or other activities as **carefully** as usual	○ 1	○ 2

20. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

- ○ 1 - Not at all
- ○ 2 - Slightly
- ○ 3 - Moderately
- ○ 4 - Quite a bit
- ○ 5 - Extremely

21. How much **bodily** pain have you had during the **past 4 weeks**?

- ○ 1 - None
- ○ 2 - Very mild
- ○ 3 - Mild
- ○ 4 - Moderate
- ○ 5 - Severe
- ○ 6 - Very severe

22. During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)?

- ○ 1 - Not at all
- ○ 2 - A little bit
- ○ 3 - Moderately
- ○ 4 - Quite a bit
- ○ 5 - Extremely

These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the **past 4 weeks**...

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
23. Did you feel full of pep?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
24. Have you been a very nervous person?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
25. Have you felt so down in the dumps that nothing could cheer you up?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
26. Have you felt calm and peaceful?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
27. Did you have a lot of energy?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
28. Have you felt downhearted and blue?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
29. Did you feel worn out?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
30. Have you been a happy person?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
31. Did you feel tired?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6

32. During the **past 4 weeks**, how much of the time has **your physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)?

- ○ 1 - All of the time
- ○ 2 - Most of the time
- ○ 3 - Some of the time
- ○ 4 - A little of the time
- ○ 5 - None of the time

How TRUE or FALSE is **each** of the following statements for you.

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
33. I seem to get sick a little easier than other people	○ 1	○ 2	○ 3	○ 4	○ 5
34. I am as healthy as anybody I know	○ 1	○ 2	○ 3	○ 4	○ 5
35. I expect my health to get worse	○ 1	○ 2	○ 3	○ 4	○ 5
36. My health is excellent	○ 1	○ 2	○ 3	○ 4	○ 5

15.2 Appendix 2: EuroQol-5 Dimensions - 3 Level version (EQ-5D-3L)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑
I have some problems in walking about ❑
I am confined to bed ❑

Self-Care

I have no problems with self-care ❑
I have some problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑
I have some problems with performing my usual activities ❑
I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑
I have moderate pain or discomfort ❑
I have extreme pain or discomfort ❑

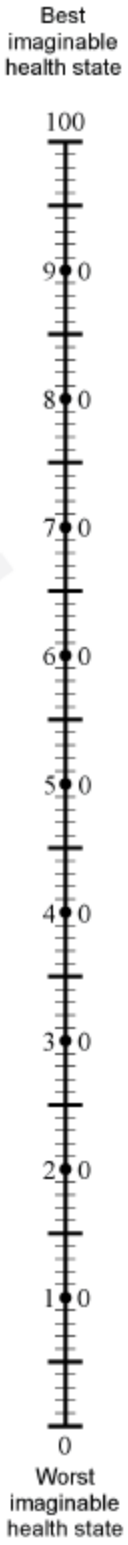
Anxiety/Depression

I am not anxious or depressed ❑
I am moderately anxious or depressed ❑
I am extremely anxious or depressed ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked **100** and the worst state you can imagine is marked **0**.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



15.3 Appendix 3: FACIT Fatigue Scale

FACIT Fatigue Scale (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

15.4 Appendix 4: Global Arteritis Activity Scale (VAS)

Could you please indicate the arteritis activity by placing a vertical mark on the line between "no disease activity" and "maximum disease activity"?

No disease activity ——————————— Maximum disease activity