ELDER

Étude observationnelle

Effet en vie réelle d'un biosimilaire de l'érythropoïétine alpha, Retacrit®, sur l'anémie chimio-induite et la fatigue à 16 semaines chez les patients âgés.

Protocole de l'étude

Hospira

Protocol for Longitudinal Observational Study

Real life effect of an epoietin alpha biosimilar Retacrit® on response to chemotherapy-induced anemia and fatigue at 16 weeks in elderly patients.

ELDER Study

Application Date	July 16, 2015
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1 - INTRODUCTION AND STUDY RATIONALE

Among around 3 million people suffering from cancer in 2012 in France, more than 270 000 patients have been treated with chemotherapy [INCA 2014]. The mean age of patients treated with chemotherapy was 62 years old [INCA 2014]. Cancer concerns mostly older people with incidence rates usually increasing with age. If taken the common cut-off of 65 years old to define the elderly, this is the fastest growing segment of population in the developed countries. So, chemotherapy is likely to be more and more used in elderly patients as seen in recent French large observational study (around 60% patients over 65 years old) [Michallet 2014].

The management of cancer in elderly is historically challenging due to a lack of prospective data regarding the effective management in this population. Elderly cancer patients have been underrepresented in clinical trials, and our knowledge on their response of chemotherapy regimens is relatively poor. Thus, a few non-profit organizations have been created, as the International Society of Geriatric Oncology (SIOG), in order to foster the development of research in the field of geriatric oncology (http://www.siog.org).

Cancer-related anemia is a cytokine-mediated disorder resulting from interactions between tumor cells and the immune system. According to a large European study, anemia (hemoglobin ‹···· 12.0 g/dl) prevalence among cancer patients is 39% and for the patients enrolling without anemia and treated by chemotherapy, it goes up to 63% [Birgegard 2005]. If untreated or improperly managed, anemia can lead to physical and functional impairment, fatigue and exhaustion being the most common symptoms [Pronzato 2010].

The cancer-related fatigue is defined as a feeling of exhaustion associated with a disproportionally high level of distress towards the patient's activity. Its prevalence rate range from 59 to 100% depending on the clinical status of the cancer, making fatigue one of the most common symptoms experienced by patients with cancer [Weis 2011, Portenoy 2000]. Patients considered fatigue as having a greater negative impact on their daily lives than many other cancer- or treatment-related complications [Harper 2005]. Although being estimated up to 70% of elderly with cancer experience fatigue, this symptom is still largely ignored in ageing population [Giacalone 2013].

The etiology of cancer-related fatigue is multifactorial and anemia is one of the etiologic identified factors. Several studies have demonstrated an association between the variation of hemoglobin level over time and fatigue intensity [Gascon 2013].

The management of anemia by Erythropoiesis-Stimulating Agents (ESAs) is well established and recommendations are clear on their use on chemotherapy induced anemia [ASCO-ASH 2002 guidelines, EORTC 2004 and ESMO 2010 guidelines]. The use of ESA is recommended as a treatment option for patients with chemotherapy-associated anemia and a hemoglobin concentration that has declined to a level ≤ 10 g/dL. Use of ESA for patients with less severe anemia (hemoglobin between 10 and 12 g/dL) should be determined by clinical circumstances. However, regarding safety, a specific attention on thromboembolic risk is required when initiating such treatments. A large European epidemiologic study reviewing data from 2,192 patients with cancer-related anemia showed judicious use of ESAs generally was safe and effective [Ludwig 2009].

In 2013, FDA made a new revision of the ESAs labeling and pointed the absence of study among patients with anemia due to cancer chemotherapy to test whether treated patients improved in exercise tolerance or functional ability. Similarly, no reliable demonstration of improved outcomes related to "quality of life" in patients receiving ESAs has been provided.

Even if the efficacy is high with ESAs, the predictability of response is quite a difficult task in chemotherapy induced anemia. If the immediacy of response to ESAs is the single most important predictor of treatment response, some other parameters such as hematological malignancy, starting hemoglobin level and age (‹···· 70 years old) are to be considered [Aapro 2009].

Numerous data demonstrate that chemotherapy-induced anemia (including mild-to-moderate anemia) has an adverse impact on quality of life that can be improved with ESAs treatment [Demetri 1998, Mäenpää 2014]. Regarding cancer-related fatigue, a large review and meta-analysis has been performed in 2008 on various pharmacological treatments which show for ESA a consistent clinically significant effect observed after 12 weeks using well validated outcome measures such as FACT-F or FACT-AN [Minton 2008].

However, anemia in elderly remains under-recognized and under-diagnosed. As increasing age is known to be associated with a poor response to ESA, there is still a need for further research into cancer-related fatigue with studies designed to evaluate if the correction of anemia could be associated with a decreased self-perceived fatigue in this older population.

A strong relation between anemia and performance status has been shown in cancer patients and that could be particularly sensitive in elderly patients [Penninx 2007]. Optimizing treatment outcomes in elderly patients with cancer will depend on careful determination of performance status as well as the potential of therapies to treat anemia in these patients [Penninx 2007]. Thus, the development of trials that address performance outcomes in addition to hemoglobin targets in this older population could be strongly needed [Merchant 2012].

Study rationale

In this context, it is planned to set-up an observational cohort study, in real-life settings, for elderly patients with chemotherapy induced anemia. This study will evaluate the effect of ESA biosimilar on both anemia and fatigue in a sixteen week period.

For the consistency of the assessment of response to treatment with an ESA biosimilar and due to a sensitive "safety" component in this population, only patients treated with Retacrit® will be selected.

Regarding fatigue questionnaire selection, FACIT-Fatigue questionnaire will be chosen due to its relevance in a non-interventional study. Conversely to the FACT-An (Anemia) questionnaire which is more useful in clinical trials and not suited to real life studies [Borget, 2007], FACIT-Fatigue is regularly used in daily practice by oncologists. Moreover, the FACIT Fatigue scale has shown strong associations with haemoglobin level, functional status, and global QOL [Yellan, 1997; Cella, 2002], which is part of our primary objective.

2 - STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to assess, in real-life settings, the effect of an ESA biosimilar (Retacrit®) on chemotherapy induced anemia response rate[a] and fatigue (FACIT-Fatigue)[b] at 16 weeks in elderly patients* (aged 70 years and over) and to confirm the possible relationship between these two criteria.

[a] Anemia response rate: the response to ESA will be assessed following EORTC guidelines (patients will be considered as responders if they do not receive a blood transfusion):

Patients with a hemoglobin increase of at least 2 g/dL compared to initial value or patient with a final value (under Retacrit®) greater than or equal to 12 g/dL.

Patients reaching the hemoglobin target value selected by the investigator at inclusion for whom the hemoglobin increase compared to initial value is greater than or equal to 1 g/dL.

[b] Fatigue: a clinically significant change in FACIT-Fatigue scale is defined as a difference superior or greater than 3-4 points compared to baseline.

* Taking into account age impact among this older population and according to the related distribution from the World Health Organization (WHO) or the French Health Agency (ANSM), patients will be split in two subgroups: 70-80 years old and ⇢ 80 years old.

2.2 Secondary Objectives

The secondary objectives are to:

- Determine the impact of an ESA biosimilar (Retacrit®) on performance status at 16 weeks.
- Assess the modalities of use of an ESA biosimilar (Retacrit®) and its safety on this specific population.

3 - TYPE OF STUDY

This is a non-interventional longitudinal, prospective, multicenter, cohort study conducted among a representative sample of public and/or private hospital-based oncologists and hematologists practicing in France.

For the study completion, each physician will see their patients in the normal course of consultations; they will not call them in for the purpose of the study.

This study will not affect the physician-patient relationship or patient management or follow-up. Physicians remain free in terms of prescriptions and follow-up procedures.

To respect the physician freedom, this study is conducted in patients for whom the therapeutic management decision is not based on their inclusion in the study.

Data will be collected by the physician during **three visits**, from the patient's medical record, questioning and clinical examination performed during these visits:

- Baseline visit – V1 initiation of Retacrit®.
- Follow-up visit – V2: 8 weeks after inclusion.
- Follow-up visit – V3: maximum 16 weeks after inclusion or 4 weeks after the last recorded dose of ESA or current chemotherapy regimen.

Data regarding the patient's fatigue will be collected directly by the patients using the FACIT-Fatigue scale filled in at each visit.

4 - CONDUCT OF THE STUDY

4.1 Recruitment of Physicians and Patients

4.1.1 Physicians selection

The study will be conducted among a representative sample of around 200 hospital-based or private clinicians with an expertise in oncology and/or hematology, practicing in France in public hospitals: CHU, CHR, CHG or Cancer Centres or Private Clinics.

Physicians will be selected from an updated general list obtained from a database as comprehensive as possible provided by the sponsor.

The selection will ensure the best sample representativeness in terms of criteria of feasibility, geographic location and distribution between the different types of institutions: CHU / CHR / CHG, Cancer Centres and Private Clinics.

A solicitation mailing explaining the study objectives and protocol will be sent to the pre-selected oncologists and/or hematologists on behalf of the Scientific Committee. The first 200 physicians who will agree to participate by mail return will form the participating physicians' population.

In case of insufficient return rate, additional telephone recruitment will be performed until obtaining a sample of around 200 physicians.

4.1.2 Patient selection

In order to limit selection bias, each physician will have to include, after site initiation, consecutive patients seen in consultation and meeting all eligibility criteria. Recruitment being competitive, physicians will be allowed to include 10 patients, with the potential to enrol more subjects upon sponsor approval, until a cohort of around 1.800 patients has been obtained.

For each patient included, information will be collected from:

- Their medical record, clinical examination and questioning during the three study visits.
- The FACIT-Fatigue scale which they will need to complete during the three study visits.

Distribution between the two age groups (70-80 years old and ⇢ 80 years old) will be checked all along the study and if needed, an orientation towards the smallest group will be applied.

4.2 Eligibility criteria

4.2.1 Inclusion criteria

To be eligible to participate in the study, patients will have to fulfil all of the following criteria:

- Patients 70 years old or above, with solid tumor, lymphoma or myeloma, seen by the oncologist and/or hematologist in the context of chemotherapy.
- Patients with anemia for whom the oncologist and/or hematologist initiates a treatment by ESA biosimilar Retacrit®.
- Patients informed about the computer processing of their medical data and their right of access and correction. An information leaflet is given to the patients by the physician and is signed by the patient.

4.2.2 Exclusion criteria

Any patient who is meeting one or more of the following criteria will not be included in this study:

- Patients with known hypersensitivity to ESA or one of its excipients.
- Patients participating in a clinical trial concerning anemia in oncology under the Loi Huriet (French clinical trial regulations) on the day of enrolment or in the preceding month.
- Patients unable to understand or fill-in French questionnaires.
- Patients refusing to participate to this study.

4.3 Study Logistics

The study logistics (preparation, organization, logistic tracking, data management and statistical analyzes) has been entrusted to the company GECEM under contract with HOSPIRA France Laboratories.

The GECEM team dedicated to this study consists of a Project Manager, a Data Manager / Statistician and Clinical Research Associates (CRAs) or monitors.

This study will be conducted in compliance with the Good Epidemiological Practices.

4.3.1 Study initiation

The study initiation will be carried out by telephone call with the clinicians who have agreed to participate after having returned and validated the financial agreement form.

The CRA or the Project Manager will contact the participating physicians to explain them the study characteristics (objectives, patient eligibility criteria, study schedule, practical modalities…), timelines and logistics.

4.3.2 Data circulation

After approval of the study protocol, each physician will be represented by a numbered site to which all documents necessary to participate in the study will be provided.

Data will be collected during three visits in a "patient observation" questionnaire completed by the physician and a self-questionnaire completed by the patient.

The Case Report Form (including for each patient: 1 "patient observation" questionnaire consisting of 3 visits: baseline and follow-up visits at 8 and 16 weeks and the relevant self-administered questionnaires) will be numbered and the number assignment will be done in chronological order.

Patients will be identified by their file number provided on the questionnaires (a random number assigned to each participating physician completed with the serial inclusion number of each patient).

After they have been completed, the CRFs will be sent using a pre-paid envelope (provided by the Sponsor) to the company GECEM which is under contract with HOSPIRA France Laboratories. GECEM will enter the date and perform CRF data verification and statistical analysis. Clarification requests will be edited and sent to the participating physician throughout the study. During the study, original documents will be archived in GECEM premises and only authorized persons will have access to them. These documents will be sent to the Sponsor for archiving. At the end of the study, the specific database will be sent in aggregate form to the Sponsor.

4.3.3 Data collection, monitoring and management

After approval of the study protocol, each physician will have a 30-month period to recruit the expected number of patients.

The total study duration planned is three and a half years from physicians recruitment up to final report.

Each physician will be asked, prior to study completion, to complete a questionnaire on his/her demographics, geographic location, specialty, type of centre in which he/she practices, and usual practices in the management of chemotherapy-induced anemia. This questionnaire will help describing the participant representativeness.

Patient enrolment

Patients will be enrolled during a routine visit. For each patient included, the physician will have to inform the patient about the study and obtain his/her consent to participate. To this end, he/she will receive an 'Information leaflet" signed by the patient (see Appendix 1).

Baseline visit – V1:

The physician will complete the inclusion form of the "patient observation" questionnaire during the consultation corresponding to the initiation of Retacrit® and hand the self-administered questionnaire to the patient, along with a prepaid envelope ("envelope T").

The physician will return to the company GECEM the inclusion form using a pre-paid envelope provided by the Sponsor.

The patient may fill in the self-administered questionnaire in the waiting room before returning it to the GECEM company using the prepaid envelope supplied.

Follow-up visit – V2:

The physician will complete the follow-up form of the "patient observation" questionnaire at 8 weeks after inclusion and hand the self-administered questionnaire to the patient, along with a prepaid envelope ("envelope T").

The physician will return to the company GECEM the follow-up form using a pre-paid envelope provided by the Sponsor.

The patient may fill in the self-administered questionnaire in the waiting room before returning it to the GECEM company using the prepaid envelope supplied.

Follow-up visit – V3:

The physician will complete the follow-up form of the "patient observation" questionnaire maximum 16 weeks after inclusion (or 4 weeks after the last recorded dose of ESA or current chemotherapy regimen) and hand the self-administered questionnaire to the patient, along with a prepaid envelope ("envelope T").

The physician will return to the company GECEM the follow-up form using a pre-paid envelope provided by the Sponsor.

The patient may fill in the self-administered questionnaire in the waiting room before returning it to the GECEM company using the prepaid envelope supplied.

5 - PROCEDURE FOR DATA COLLECTION

5.1 Patient Information Leaflet

Before initiating any procedure related to the study, the participating physician will have, in a clear and understandable manner, to inform the patient on the study and obtain his/her consent to participate. To this end, he/she will receive an 'information leaflet" (see Appendix 1) to be given and signed by the patient. The latter specifies the type of information to be collected, persons who will receive the data, right of access, correction and opposition to processed data.

5.2 Nature of collected data

Each patient data will be recorded in a CRF provided to the physician by the Sponsor. This CRF will include one "patient observation" questionnaire consisting of 3 visits: baseline, follow-up at 8 weeks and at 16 weeks visits and the relevant self-questionnaires.

No data that directly names the persons involved will be collected. Only a patient record numbering linked to the physician site number will ensure the proper record monitoring and allocation.

5.2.1 Patient observation questionnaire completed by the physician

The following data will be collected:

At baseline – Initiation of Retacrit® - V1

- Demographics: age, gender, weight, height.
- Vital signs: blood pressure, heart rate and performance status.
- Screening tool to identify older cancer patients requiring geriatric assessment (G8 questionnaire) [Soubeyran 2011].
- Medical history and risk factors: venous thromboembolism, cardiovascular, other…

- Data on tumour: date of diagnosis, location, stage of the disease.
- History of chemotherapy and anemia including blood transfusion in the past year.
- Chemotherapy regimen: line treatment, protocol, number of cycles and duration of the cycle, treatments and doses.
- Hematology (hemoglobin, red cells count, mean cell volume, hematocrits, platelets, leukocytes, lymphocytes, polynuclear neutrophils), biochemical parameters (serum folate, Vitamin B12, CRP (C-reactive protein), Albumin, Creatinine clearance) and iron status.
- Treatment modalities for Retacrit®: dose, administration route and planned duration.
- Associated treatment: Iron (dosage, route) and supportive treatments.

At follow-up during chemotherapy (8 weeks) – V2

- Vital signs and disease progression: performance status.
- Evaluation of anemia (hemoglobin) and iron status.
- Change in chemotherapy regimen if applicable.
- Details of the treatment by Retacrit®.
- Safety: SAE, AE, treatment discontinuation and cause.

At Follow-up visit – V3 – maximum 16 weeks after inclusion)

- Vital signs and disease progression: performance status.
- Evaluation of anemia and determination of response (according to EORTC criteria).
- Iron status.
- Change in chemotherapy regimen if applicable.
- Blood transfusion required during the study.
- Details of the treatment by Retacrit®.
- Safety: SAE, AE, treatment discontinuation and cause.

5.2.2 Patient self-questionnaire

At baseline (V1), Follow-up V2 and V3 visits

- Fatigue assessed by a validated questionnaire (FACIT-Fatigue [Cella 2011]).
- Quality of life assessed by a validated questionnaire for cancer patients aged ≥ 70 years (QLQ-ELD 14) [Wheelwright 2013].

At baseline (V1)

- Depression and anxiety assessed by a validated questionnaire (HAD, Hospital Anxiety and Depression Scale [Zigmond 1983].

5.3 Quality Control

Upon receipt of the completed CRF(s) by GECEM and until study result analysis, the quality control will be performed in accordance with the current standardized operating procedures. The documents received will be processed according to the following procedure: stamping indicating the receipt date, then recording on a specific study database.

A quality control will be carried out systematically on the CRFs received, especially for missing or incomplete pages in order to contact the physician if necessary.

The controlled CRF will be provided to the Data Management Department.

An on-site audit may be carried out in 5-10% of participating centers to ensure coherence and quality of data collected by the physician.

6 - STUDY OVERSIGHT

6.1 Scientific Committee

A Scientific Committee has been formed by HOSPIRA France, with the task to validate the scientific quality of the project, define and/or validate the study methods and procedures, review and validate the statistical analysis plan and report the study results, and validate request for amendment.

The Scientific Committee will also be asked to advise HOSPIRA France on how to ensure the quality of the collected data.

The Scientific Committee is composed of the 6 following members:

Doctor Matti AAPRO - Oncologist - Clinique de Genolier – Suisse

Doctor Etienne BRAIN - Oncologist – Institut Curie – France

Professor Claire FALANDRY - Oncologist – CH Lyon Sud – France

Doctor Djamel GHEBRIOU - Oncologist - CH Argenteuil - France

Professor Jean-Emmanuel KURTZ - Oncologist - CHU Hautepierre - Strasbourg - France

Doctor Hélène ALBRAND – HOSPIRA France

6.2 Study Sponsor

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6.3 Study Monitor

GECEM

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7 - DATA MONITORING, ENTRY AND CONTROL

7.1 Study monitoring

A study-specific management database will be developed for study monitoring and will allow editing regularly the progress state. A weekly reporting will be performed according to the progress states defined with the Sponsor at study initiation.

The CRA or monitors will then follow the participating physician in answering their questions, by performing a regular telephone follow-up for file completion and returning, and by dealing with physician requests on incomplete data, inconsistencies, ranges, non-responses and omissions.

A hotline will be available from 9 am to 6.30 pm, from Monday to Friday, during the entire study duration to respond to physician requests.

Hotline n°: +33 (0)1.55.58.95.05

7.2 Data entry

A study-specific database will be created, tested and validated prior to data entry. A plan for data validation will be developed before database locked and will describe in detail the controls to be performed for each variable and the list of corresponding corrective actions (obvious corrections authorized, clarification requests for the physicians).

The CRF data will be entered twice then controlled by the team responsible for data management using the error messages from validation programs. The database will be locked after a quality control on a random sample of n +1 questionnaires and self-questionnaires (n being the number of questionnaires and self-questionnaires).

8 - STATISTICAL METHODS PLANNED

8.1 Number of Patients and Physicians

Number of Patients

The primary endpoint is to assess, in real-life settings, the effect of an ESA biosimilar (Retacrit®) on chemotherapy induced anemia response rate and fatigue (FACIT-Fatigue) at 16 weeks in elderly patients (aged 70 years and over) and to confirm the possible relationship between these two criteria.

It will be assessed in both subgroups (two subgroups: 70-80 years old and ⇢ 80 years old) and in global population.

This primary objective focused on anemia response rate and fatigue evolution.

Regarding Anemia:

The response to ESA will be assessed following EORTC guidelines. Will be considered as responders without blood transfusion:

- Patients with a hemoglobin increase of at least 2 g/dL compared to initial value or patient with a final value (under Retacrit®) greater than or equal to 12 g/dL.
- Patients reaching the hemoglobin target value selected by the investigator at inclusion for whom the hemoglobin increase compared to initial value is greater than or equal to 1 g/dL.

According to the recently French published cohort with ESA biosimilar in similar indication [Michallet 2014], a response rate of 81.6% has been reported after 3 month on general population with a mean age of 66 years.

In our study, considering our older population (70 years old and above) where a potentially less effective response [Aapro 2009], we anticipate a response rate around 65 - 70%.

Based on this hypothesis, 588 patients are needed to assess a 65 to 70% with an absolute precision of 4.0%.

Regarding fatigue:

A clinically significant change in FACIT-Fatigue scale is defined as a minimum difference of 3-4 points over time [Webster 2003, Cella 2002]. This has been shown in mixed-diagnosis-cancer patients both in patients in chemotherapy-induced fatigue [Cella 2002] and in patients treated with epoetin alfa for chemotherapy-induced anemia [Demetri 1998]. In these studies, the FACIT-Fatigue change scores over time were observed with a standard deviation around 12, regarded as acceptable.

With this standard deviation around 12, the number of 588 subjects will allow to describe a mean change in FACIT-Fatigue score of at least 4 with a sufficient precision of ± 0.97.

According to previous data with ESA biosimilar [Michallet 2014], we can anticipate this distribution:

- 65% of patients between 70 - 80 years old,
- 35% of patients above 80 years old.

Taking into account the subgroups distribution mentioned above, a minimum of 588/0.35 = 1680 patients will have to be included.

Anticipating about 8 % of possible missing or useless data, the number of patients to include will be 1800.

Number of Physicians

Physicians' recruitment will be carried out from a comprehensive external list of oncologists and/or hematologists practicing in France at a national level.

Each physician will be asked to include 10 patients, this number being a good compromise between study needs and enrolment capacities of each centre. Sites may be permitted to enrol more than 10 patients upon sponsor approval.

To involve a sample of clinicians as representative as possible with an expertise in oncology and/or hematology and to allow forming such a cohort of 1800 elderly patients with tumour over a 30-month period, around 200 oncologists and/or hematologists are expected to participate to the study.

8.2 Statistical Methods Planned

The detailed statistical analysis plan will be developed by the company GECEM and validated by the Sponsor and the Scientific Committee before database lock.

8.2.1 Study populations

The following populations will be defined:

- Safety population: all patients who received at least one dose of Retacrit®.
- Analysis population: all patients who received at least one dose of Retacrit® and having a follow-up Hb or FACIT-Fatigue at end of Week 8 or Week 16.
- Descriptive Analysis

The statistical analysis will be performed using S.A.S.® Software version 9.3 (or higher), SAS Institute, NC, Cary, USA.

A statistical analysis plan will be finalised and approved by the Sponsor and the Scientific Committee before the locking of the study database.

Descriptive statistics of all collected data will be presented.

- Quantitative variables will be described (distribution) in terms of numbers, missing data, mean, standard deviation, median and range.
- Qualitative variables will be described (distribution) in terms of absolute frequency and percentage per class. The percentage of each type of response will be provided when the variable can take different forms (treatments, adverse events...). The number of missing data will be provided for each variable (the missing data will not be included in the calculation of percentages).

In case of comparative analysis, it will be performed with a significance level set at 5% using:

- The Pearson Chi2 test for qualitative variables.
- The Student t-test or ANOVA for Gaussian quantitative variables.
- The non-parametric Mann-Whitney or Kruskal-Wallis test for semi-quantitative or non-Gaussian quantitative variables.

8.2.2 Analysis of the Primary Objective

The analysis of the primary objective will be performed on the analysis population.

The effect of an ESA biosimilar (Retacrit®) on chemotherapy induced anemia response rate and fatigue (FACIT-Fatigue) will be described in both subgroups (two subgroups: 70 - 80 years old and ⋯› 80 years old) and in global population with its 95% confidence interval.

The effect of Retacrit® on chemotherapy-induced anemia response rate will be assessed from the questionnaire completed by the physician during the baseline, at week 16 or both at Week 8 and Week 16.

The fatigue will be assessed using the FACIT-Fatigue Scale completed at each visit. This questionnaire measures an individual's level of fatigue during their usual daily activities over the past week and has been validated for use with older adults [Tennant 2012]. It is a short, 13-item, easy to complete (in 5–10 minutes) questionnaire. Moreover, it has shown strong associations with haemoglobin level, functional status, and global quality of life [Yellan 1997, Cella 2002].

A $_2$ test will be performed to detect a relationship between anemia response rate (target value) and fatigue improvement assessed by FACIT-Fatigue score (delta of 4 points or more).

8.2.3 Analysis of Secondary Objectives

The analysis of the secondary objectives will be performed on the analysis population (except for the tolerance).

Secondary objectives will be described globally and by subgroups:

1. The impact of Retacrit® on performance status will be described from the questionnaire completed by the physician during the follow-up and final visits.

2. The modalities of use of Retacrit® will be described from the questionnaire completed by the physician during the baseline, follow-up and final visits.

3. The tolerance to treatment with Retacrit® will be assessed from the questionnaire completed by the physician during the follow-up and final visits. This analysis will be performed on the safety population.

The adverse effects will be encoded using the MedDRA dictionary (current version at the time of the encoding) and analyzed using the following classification levels: “System Organ Class” (SOC) and “Preferred Term” (PT).

Will be described for the total population and by subgroups, 70 - 80 years old and ⇢ 80 years old:

- Number and percentage of patients having experienced at least one adverse event severe or not.
- Number and percentage of patients having discontinued the treatment and the reason why.

8.2.4 Presentation of Results

The CSR report will be written in accordance with ICH after discussion of results with the Scientific Committee and potential additional analysis.

8.2.5 Management of Missing Data and Inconsistencies

In case of missing data or inconsistencies, requests for corrections will be edited and sent to the physician.

Control data and requests will be carried out throughout the study.

9 - PHARMACOVIGILANCE

9.1 Definitions (Article R.5121-152 of the French Public Health Code)

The definitions below are the general definitions of terms. For the purpose of this study, only Serious Adverse Events and Adverse Events of Special Interest will be collected.

Adverse event

Harmful and unexpected reaction to a drug or product mentioned in Article R.5121-150.

Serious adverse event

A serious adverse event is any untoward medical occurrence resulting in death, being life threatening, requiring inpatient hospitalization or prolongation of existing hospitalization, resulting in persistent or significant disability/incapacity or in congenital anomaly/birth defect.

Any adverse event considered as serious by the health professional but being not mentioned in this regulatory definition can also be considered as a serious adverse event. Decree dated June 10, 2011 of Good Pharmacovigilance Practices.

Misuse

Intentional and inappropriate use of a drug or product in relation to the authorized or prescribed dose, route, indications or use not in compliance with the terms of the marketing authorization or registration and with the Good Practice guidelines.

Overdose

Administration of a dose of drug or product, per intake or per day, which is greater than the maximum dose recommended in the product characteristics mentioned in Article R.5121-1. The cumulative effects due to overdose are taken into account.

Abuse

Persistent or sporadic, intentional excessive use of a drug or product mentioned in Article R.5121-150, accompanied by harmful physical or psychological reactions.

Medication error

Unintentional error of a health professional, patient or third party occurred during the care pathway, involving a drug or health product mentioned in Article R.5121-150, including at the time of the prescription, dispensation or administration.

Occupational exposure

Exposure to a drug or product mentioned in Article R.5121-150 during the medical practice.

9.2 Procedure for Reporting Adverse Events

According to the current legislation (Decree n°2012-1244 dated November 08, 2012), **any Adverse Event** likely to be due to a drug taken by a patient included in this research must be immediately reported to the Regional Pharmacovigilance Centre (RPVC) of which the physician depends or to the drug MAH laboratory depends.

Adverse events must be reported using the pharmacovigilance reporting form which can be downloaded from the ANSM website: http://www.ansm.santé.fr/.

The physician undertakes to fulfil his/her reporting obligations concerning the pharmacovigilance of the products used in this study and to inform within a maximum period of 24h the person responsible for the pharmacovigilance at HOSPIRA France of any adverse event or other information relevant to the PharmacoVigilance related to **Retacrit®** occurred during the study.

The person is **Mr Bruno BÉCHADE**, Head Pharmacist, and any pharmacovigilance information shall be sent to him:

By e-mail to « **affaires.reglementaires.fr@hospira.com** »

And/or by fax: **+331 40 83 86 09**.

And/or by mail: Hospira France Pharmacovigilance

17-19 Rue Jeanne Braconnier - 92360 MEUDON LA FORET

If necessary, the physicians could also directly call the Pharmacovigilance Department at HOSPIRA France: **+331 40 83 86 08**.

Any adverse effect of special interest listed below must be notified by the physician to the Pharmacovigilance Department at HOSPIRA France:

- Pure red cell aplasia (PRCA) or erythroblastopenia,
- Neutralizing antibodies,
- Thromboembolic events, including cerebrovascular events (e.g. stroke, cerebral haemorrhage, cerebral infarction, transient ischemic attack), deep vein thrombosis, myocardial infarction and pulmonary emboli,
- Lack of effectiveness,
- Off-label use.

Any case of pregnancy during treatment with Retacrit® must be documented by the physician in the CRF and in the appropriate pharmacovigilance form “Pregnancy” or “Following childbirth”. This form must be sent within a period of 24 hours to Hospira France using the same procedures described above.

Pregnancies will be followed through knowledge of the final outcome. The babies will be followed for at least 8 weeks after delivery.

The evolution of all SAE: resolution, worsening... will be followed, documented using a follow-up report and will be reported to the competent authorities in accordance with the current procedures.

10 - REGULATORY PROCEDURES

10.1 Patient Privacy and Information

The data collected in this study will be processed by computer in conditions which will ensure their confidentiality by encoding in strict respect for medical confidentiality.

In application of Articles 34 and subsequent of the Act dated January 6, 1978, amended by the Law 2004-801 dated August 6, 2004, referred as "Data Protection Act", patients will be informed of their right of access and correction of their data which are processed by computer.

10.2 Declaration to the Advisory Committee on Information Processing for Research in the Field of Health (French CCTIRS), and the National Committee for Data Protection (French CNIL) (Justification for Using Personal Data).

This study has been subject to authorization from the Advisory Committee on Information Processing for Research in the Field of Health (Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé or CCTIRS) on 30 April 2015.

Physicians

Personal data concerning the participating physicians will be processed by computer and the list of all physicians have been declared to the National Committee for Data Protection (Comité Nationale de l'Informatique et des Libertés or CNIL). Each participating physician has, in application of Articles 39 and subsequent of the Law dated January 6, 1978, called "Data Protection Act", modified by the Law dated August 6, 2004, a right of access and correction of this file. Thus, he/she will be entirely free to use it with the Sponsor or company GECEM if necessary.

Patients

Data concerning patients will be collected in a strictly non identifying manner. No patient name will be reported on the study files, especially on the CRF. Only an encoding allowing controlling data entry and physician remuneration will be used. It will be a random number assigned to each physician completed with the serial inclusion number of each patient.

There will be no interconnection between the physician database, for administrative purposes, and the indirectly personal patient database, for statistical analysis.

A request for authorization from the CNIL will be submitted after opinion of the CCTIRS, for computer processing of personal data intended for implementing the observational study.

The participating physician will have to inform each patient that his/her data will be collected so as to ensure their confidentiality by encoding in order to be used in an observational study. To this end, he/she will be provided with an information leaflet to give to each patient selected (see Appendix 1).

10.3 Declaration to the Institutional Review Board (French Comité de Protection des Personnes or CPP) (Justification for Non-Application of the French Public Health Law).

This study will not include any directive on patient management. It will not affect the clinician-patient relationship, it will therefore be outside the scope of the regulation which applies to biomedical researches (Decree n° 2006-477 dated April 26, 2006 modifying the section I of the title II of the Book I of the first part of the French Public Health Code related to biomedical researches).

Consequently, a request for CPP opinion is not necessary.

10.4 Declaration to the French National Council of the Order of Physicians (French CNOM)

The physicians will be granted with a remuneration. To this end, a declaration will be submitted to the French National Council of Order of Physicians (Conseil National de l'Ordre des Médecins or CNOM), in accordance with the Article L.4113-6 of the French Public Health Code before the Sponsor HOSPIRA France will initiate the study.

Each physician will receive three copies of the financial convention of which one will have to be sent by him/herself to the County Council of the Order of Physicians of which he/she depends (Article L.4113-9 of the French Public Health Code).

In accordance with the Law n°2011-2012 dated December 29, 2011, on the strengthening of drug and health products safety and the Decree n° 2013-414 dated May 21, 2013 on the transparency of the remuneration granted by companies producing or marketing products for health or cosmetic purpose for humans, the Sponsor is required to publish on a public website and submit to the CNOM for publication, the remunerations (kind or cash) granted to health professionals or associations representing them and the existence of agreements that the Sponsor concludes with the latter within 15 days following the agreement signing.

10.5 Agreement of the participating physicians

This protocol will be presented to the prospective clinicians prior to ask them confirmation of their participation. Their participation will be confirmed upon signature of the financial agreement proposed by HOSPIRA France.

In accordance with the Article R.5121-13 of the French Public Health Code, clinicians and any individual who might participate in the study are subject to professional confidentiality with regard to the implementation procedures, participating individuals and results obtained. They can only, after Sponsor authorization, provide information on the study to the Minister of Health, Public Health Medical Inspectors, Public Health Pharmacist Inspectors, General Director and Inspectors of the Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM).

10.6 Financial Agreement

The study physicians agree to comply with the protocol as written.

This acceptance is contractual and the financial agreement between the company GECEM, in name and on behalf of HOSPIRA France, and each physician, will mention the remuneration planned.

10.7 Audits and Inspections from Health Authorities

If notified in advance, the physician agrees to submit all documents and information used and/or generated in the study course to duly authorized representatives of the Sponsor and/or representatives of national or international Regulatory Authorities so that they can be subject to verification/audit during or after the end of the study.

He/she will have to cooperate in the audits organized by the Sponsor or on its behalf and inspections by the national or international Regulatory Authorities.

11 - ARCHIVES

The study documents will be archived by the Sponsor in accordance with its procedures and the current legal and regulatory provisions. The physicians will not be asked to archive the study documents.

12 - CSR AND PUBLICATIONS

The results will be reported in an analysis report validated by the Scientific Committee and the Sponsor HOSPIRA France and will be sent in condensed visual format to the participating physicians after validation. The CSR report will be written according with ICH.

The results will be submitted for publication in a peer-reviewed journal.

The procedures for scientific result publication and authors involved in these publications and communications will be defined by the Sponsor which reserves the worldwide copyright of all important publications, including translations into other languages.

The Scientific Committee will take part in communicating the study results.

The Sponsor reserves the rights to:

- Use the study results for any regulatory procedure, on its own behalf or that of subsidiaries.
- Present the results in its medical information letter on drugs.
- Distribute reprints of the publications.

No one may use these rights without the prior written authorization of the Sponsor.

13 - PHYSICIAN STUDY FILE CONTENT

Each participating physician will receive the following documents:

- Three copies of the financial agreement: one copy for the County Council of the Order of Physicians, one for HOSPIRA France and one for the physician.
- A copy of the scientific protocol.
- One CRF and one information leaflet (reference to the CNIL) per patients to be included.
- Pre-paid envelopes to return the documents.

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15 - APPENDIX

15.1 Patient Information Leaflet

Information note (to be given to the patient)

Elder Study

Real life effect of an epoietin alpha biosimilar Retacrit® on response to chemotherapy-induced anemia and fatigue at 16 weeks in elderly patients.

Dear Madam, Sir,

Your clinician proposes you to participate in a national observational study sponsored by HOSPIRA France laboratories.

The objective of this study is to describe, in routine practice, the effect of an Erythropoiesis-Stimulating Agent biosimilar (Retacrit®) on anemia and fatigue in elderly patients receiving chemotherapy and to confirm the possible relationship between anemia and fatigue.

This study is conducted among 200 oncologists and/or hematologists and a cohort of 1800 patients who will be followed for 16 weeks will be formed.

It presents no constraints for you and does not change the management of your treatment by your clinician. No particular additional examination or treatment apart from those usually used by your clinician will be required.

If you agree to participate in this study, your clinician will collect information about your medical history, disease management, the chemotherapy protocol that you received, erythropoietin treatment modalities and data from additional examinations collected for his/her usual practice.

You will be asked, in the context of this study, to fill three questionnaires relating to your fatigue (the FACIT-Fatigue questionnaire) and your quality of life (the QLQ-ELD14 questionnaire). Moreover, you will be asked to fill a questionnaire relating to your mood (the HAD sale) only at the inclusion visit,

You are free to refuse to participate in this study and, at any time, to withdraw your participation. Your refusal will not change your relationship with your clinician or the quality of the care which will be provided.

Your data collected in this study will be processed by computer in conditions which ensure their confidentiality by encoding in strict respect for medical confidentiality.

In accordance with Article L.1122-1 of the French Public Health Code, when the study has ended, if you wish, you will be personally kept informed of the overall results by your doctor as soon as these are available.

This study has been declared to the National Committee for Data Protection (Comité Nationale de l'Informatique et des Libertés or CNIL).

In application of the Law dated January 6, 1978, referred as « data protection act », modified by the Law dated August 6, 2004 for individual protection regarding personal data processing, we inform you that you have a right of objection, access and correction of these data that you can exercise at any time by contacting your clinician who proposed this study and who will communicate your request.

Thank you for your attention. We have the honour to be, Madam, Sir, yours faithfully.

The Scientific Committee

Physician stamp	**Patient** Date: ..... Date: ..... Name of patient: ..... Signature:

Promoteur

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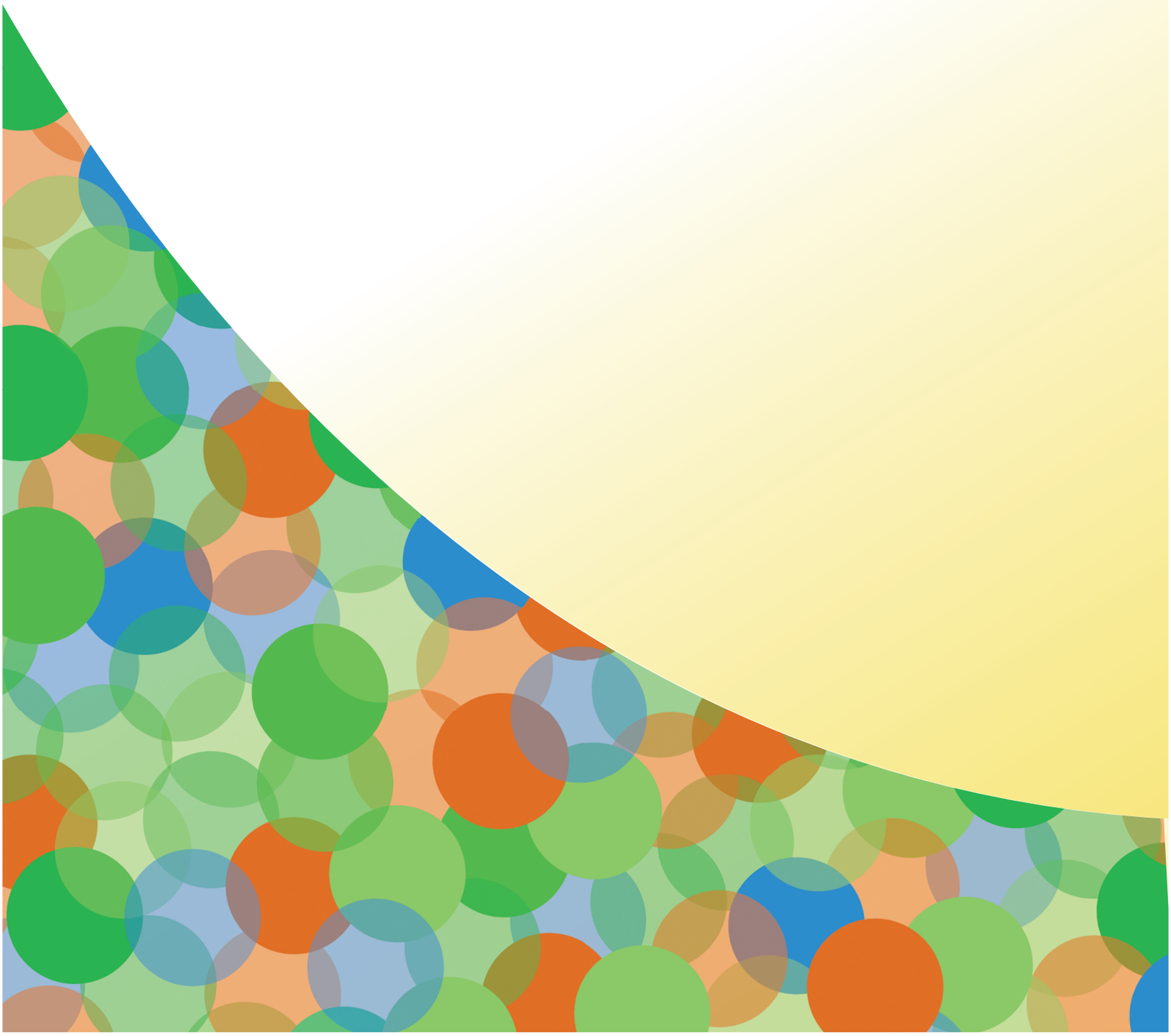

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