ESCORT-HU

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Confidential

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Protocol Synopsis

Name of Sponsor : Addmedica	Name of finished product : Siklos®	Name of active ingredients : Hydroxycarbamide
Title of study	ESCORT-HU : European Sickle Cell Disease Cohort - Hydroxyurea.	
Investigators	Physicians experienced in the management of sickle cell disease (SCD); treating physicians.	
Study centres	France, United-Kingdom, Greece. Other European countries will be encouraged to participate as soon as Siklos® becomes available in their country.	
Trial duration	Up to 8 years recruitment, to get at least 2 years follow-up. Total expected duration : 10 years	Non-interventional follow-up cohort study.
Objectives	In the context of the Risk Management Plan (RMP), as requested from Addmedica by the EMA, to collect information about long-term safety of Siklos® (hydroxycarbamide) when used in patients with Sickle Cell Disease, assessed on : • Frequency of : ➢ myelosuppression (requiring permanent or temporary discontinuation of therapy) secondary to hydroxycarbamide-induced myelotoxicity ➢ malignancies, skin ulceration and impaired postnatal development (growth). ➢ amenorrhea, fertility impairment • Safety in nominated sub-populations : ➢ young patients (children, adolescents until end of puberty) ➢ elderly patients ➢ patients with underlying SCD-related hepatic or renal impairment ➢ pregnancy and its outcome, particularly for congenital malformations ➢ concomitant use of hydroxycarbamide and specific therapies : o HIV drugs especially Nucleoside Analogue Reverse Transcriptase Inhibitors (NRTI) o other myelosuppressive agents o radiation therapy o concomitant use of live vaccines Other points of concern are : • Overall mortality and survival time. • Occurrence of SCD events, in particular : ➢ painful crises ➢ acute chest syndrome ➢ stroke ➢ acute splenic sequestration ➢ infections	

Name of Sponsor : Addmedica	Name of finished product : Siklos®	Name of active ingredients : Hydroxycarbamide
Methodology	Multicentre, prospective, non-interventional cohort study in patients with SCD treated with Siklos® and followed-up for up to ten years. All patients prescribed Siklos® within 8 years of its commercialisation until reaching at least 2000 patients will be enrolled in this cohort. The follow-up of these patients will be strictly observational and will fit within their usual clinical monitoring without any controlled treatment, specific exam or modification of their follow-up, in compliance with the SPC of this orphan product. Patients' data could be collected retrospectively especially when the patient started Siklos before being enrolled in the study. Patients will be evaluated at inclusion, then every 1 to 4 months, according to normal monitoring of the disease and to the recommendations of Siklos® specification for use. A minimum of a yearly follow-up will be requested. Patients will be informed by their initiating physician about the study and enrolled in case they agree to participate. Solely physicians experienced in the care of SCD (reference centres) are legitimated to initiate a Siklos® treatment; follow-up is authorised by both initiating and treating physicians.	
Number of subjects	Around 2000 patients treated with Siklos®. The number of subjects is determined taking into account 20% of severe SCD on an overall 24 000 estimated number of subjects with the disease in Europe, and approximately 50% of these on Siklos®. This will allow for an estimation of frequencies of events as low as 0.5% with a precision of 0.2%.	
Diagnosis and main criteria for recruitment	• Male or female ambulatory patients, aged 2 years and more (children, adolescents or adults) • With symptomatic sickle cell syndrome • Treated with Siklos® • Having been informed of the study by the initiating physician and consenting to participate to the cohort.	
Test product, dose and mode of administration	Siklos®: 15 to 30 mg/kg/day usual dosage and 35 mg/kg/day as Maximum Tolerated Dose (MTD). Starting dosage: 15 mg/kg/day; to adjust by steps of 5 mg/kg/day according to clinical and haematological response.	
Duration of treatment	Permanent	
Reference product, dose and mode of administration	Not applicable	

Name of Sponsor : Addmedica	Name of finished product : Siklos®	Name of active ingredients : Hydroxycarbamide
Criteria for evaluation	**Safety** The primary safety parameter is the occurrence of adverse events and serious adverse events, specifically: • Frequency of malignancies • Frequency of skin ulceration (broken out by severity) • Frequency of myelosuppression requiring temporary or permanent discontinuation of Siklos®. The secondary safety parameters are: • Effects of Siklos® on growth development : specific examinations (scintigraphy, radiography, …) if the difference with the normal growth is upper than 2 standard deviations • Outcome of pregnancies: rates of miscarriage, stillbirths, APGAR score at birth, congenital malformations • Any occurrence of an unforeseen safety pattern. A special focus will be given to specific population, *e.g.*, elderly patients, patients with renal or hepatic impairment, HIV patients, patients receiving live vaccine, patients treated with other myelopsuppressive products or with radiotherapy, … **Siklos® effects** : • Overall mortality and survival rates • Frequency of SCD events : ➢ painful crises ➢ acute chest syndrome ➢ stroke ➢ acute splenic sequestration ➢ infections • Hospitalisations due to SCD events • Frequency of blood transfusions.	

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Data collection

Data will be collected through electronic media. The list of data is not limited to the foreseen ones listed below and may be increased according to interest or emergent patterns.

Baseline data will include :

- Demographic characteristics (date of birth, gender, height, weight), occupation
- SCD history :
  - Type of expressed Hb : HbSS, HbSC, HbSβ^0 or HbSβ^+
  - Neonatal screening of the disease
  - Date (or year) of first appearance of SCD symptoms
  - Date (or year) of SCD diagnosis
  - History of SCD manifestations :
    - history of growth delay
    - infections
    - number and type of vaso-occlusive complications : acute chest syndrome, priapism, stroke, hepatopathy, acute splenic sequestration, skin ulceration, other
    - number of hospitalisation in relation with SCD
- Presence or absence of skin ulceration
- Any history of malignancy (type, location, date, resolution)
- Classical clinical examination (cardiovascular, respiratory, digestive…)
- In males whether sperm had been examined
- In females obstetric history, especially amenorrhea (if applicable)
- Treatment history data :
  - Blood transfusions
  - History of treatment by hydroxycarbamide (other than Siklos®) will be also documented : start, end dates, last dose
- Siklos® treatment initiation : date of start treatment, dose
- Live vaccines
- Other relevant concomitant conditions and associated treatment
- Biological data : current haemoglobin, MCV, HbF, ferritin, white cell count and differential, platelets, urinalysis (protein), liver function tests, blood urea and creatinine.

Baseline data will be collected as far as possible for all symptomatic SCD patients screened to enter the cohort.

Name of Sponsor : Addmedica	Name of finished product : Siklos®	Name of active ingredients : Hydroxycarbamide

	Follow-up data are not limited to those listed below : • Demographic data : height, weight • Growth, school, occupation • Presence or absence of skin ulceration • Malignancy (type, location, date, resolution) • Pregnancy • Other concomitant pathologies/adverse events not related to sickle cell disease, with description, seriousness, start and end date, outcome, severity, relation with previous pathology, ancillary examination, treatments, relationship to Siklos® • Events related to sickle cell disease with description, start and end date, severity, outcome, new transcranial Doppler (if any) • Classical clinical examination • Biological data: at least blood count, liver function tests, blood urea and creatinine • Follow-up of Siklos® treatment • Concomitant medication, in particular : ➢ HIV drugs (NRTI) ➢ Myelosuppressive agents ➢ Radiotherapy ➢ Live vaccines • Infections • Number and type of SCD events : ➢ Painful crisis ➢ Acute chest syndrome ➢ Priapism ➢ Stroke ➢ Hepatopathy ➢ Acute splenic sequestration ➢ Other • Number of hospitalisation in relation with SCD • Treatment discontinuation or withdrawal, and reasons.
Statistics	All statistical analyses will be performed at the 5% significance. Parameters will be summarized using mean, median, standard deviation, range for continuous data and counts or percentages for categorical data. Descriptive statistics will be used to : • Report the prevalence of primary and secondary parameters. • Describe the global population and the sub-populations. Appropriate multivariate analysis will be used to describe the determinants of the observed events. Regular interim reports will be issued in accordance with the PSUR schedule (twice a year), in accordance with the RMP. The report will present a general description of the population included and frequencies of all primary and secondary parameters on the global population. Sub-population analyses will be performed when the collected data on the same parameters will be sufficient.

Glossary of abbreviations and definition of terms

AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
CI	Confidence Interval
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organisation
EC	Ethics Committee
EMA	European Medicines Agency
Hb	Haemoglobin
IRB	Independent Review Board
MedDRA	Medical dictionary for Regulatory Activities
NA	Not Applicable
PSUR	Periodic Safety Update Reports
RMP	Risk Management Plan
SAE	Serious Adverse Event
SCD	Sickle Cell Disease
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedures

Investigators and study administrative structure

Sponsor

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Steering Committee

A Steering Committee will comprise medical experts involved in the cohort follow-up, the sponsor, and an independent epidemiologist. The Steering Committee will oversee the conduct and reporting of the cohort follow-up, assuring expert clinical guidance and a high standard of scientific quality, reviewing all SAEs and clinical endpoints reported by the sites (*i.e.*, initial diagnoses, laboratory values, results of procedures) to determine the occurrence of clinical issues, and proposing any necessary protocol amendments to be submitted to health authorities.

The number of representative of each country will be linked to the prevalence of SCD in the country. Presently it is foreseen to have 4 representatives for United-Kingdom and France and 2 for Greece

The Steering Committee Charter will define the responsibilities of the committee.

Members of the committee will be determined according to their skills, number of patients included in their center, availabilities for meeting and interest in participating.

European Clinical Board Committee (ECBC)

A least one of the physicians specialised in SCD of each country in Europe is recruited to participate to the ECBC, the missions of which are the following ones:

- To animate the cohort follow-up in each country and ensure its development
- To propose and decide on development of the action to set up.

The European Clinical Board Committee charter will define the responsibilities of the committee.

Contract research organisations

Pharmacovigilance	**For Drug Consulting** 6 Rue Rouget de Lisle 92240 Malakoff
Qualified Person for Pharmacovigilance	**Dr Corinne Duguet** Phone : +33 (0)1 72 69 01 86 Fax : +33 (0)1 73 72 94 13 email : corinne.duguet@addmedica.com

Trial management (data collection and on-site quality control)	**Peter Holmes Clinical (November 2007 to September 2014)** 65 rue Paul Eluard 93200 Saint Denis FRANCE **Keyrus Biopharma (since March 2015)** 18/20 rue Clement Bayard 92300 Levallois-Perret FRANCE **Outsourced CRAs** • Caroline Dumas Reseaulution society 34 bis rue Parmentier 92800 Puteaux FRANCE • Hervé Perrier (Freelance CRA) • Sophie Armand (Freelance CRA)

Database host	**Arone** 4, rue Leroux 94100 SAINT-MAUR DES FOSSES FRANCE

Statistics	**Inferential** 35, rue Godot de Mauroy 75009 Paris FRANCE

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1 Introduction and study rationale

Sickle cell disease (SCD) is an autosomic recessive hereditary disease involving the haemoglobin S (HbS). SCD disease is present in HbS homozygote patients (HbSS). It is also present in heterozygote patients expressing HbS, HbC, (HbSC) and during β-thalassemia (HbS-β-thalassemia patients). SCD severity varies depending on the Hb expressed haplotypes (Table 1).

Table 1: Impact of Hb type expressed on SCD severity

HbSS	HbSC	HbSβ°	HbS β$^+$
Severe	Moderate	Severe	Moderate

The clinical manifestations of SCD result primarily from haemolytic anaemia and effects of repeated intravascular sickling, causing vaso-occlusion and ischemic injury. Chronic organ damage in SCD is an insidious process that may affect almost every organ system and can lead to considerable morbidity and mortality at an early age. Loss of splenic function, sickle nephropathy (proteinuria and renal failure), pulmonary hypertension, and brain ischemic lesions are examples of long-term end-organ damage observed in SCD[1,2,3,4]. The commonest disorder of SCD is painful vaso-occlusive crisis, followed by infection and acute chest syndrome (ACS), occurring in up to 40% of patients and commoner in children. ACS is characterised by episodes of chest pain, fever, leukocytosis, and uni-or bi-lateral pulmonary infiltrates. Other manifestations of SCD include:

- Stroke (with a high frequency in children in their first decade)
- Priapism (associated with a risk of future impotence)
- Infections
- Aplastic crisis (often caused by parvovirus infection)
- Acute bone marrow infections
- Sequestration crises
- Major organ damage to the heart, lungs, kidney, eyes, and femoral heads.

Splenic sequestration predominantly occurs in children with homozygous HbS and is a life-threatening complication. Renal organ damage may lead to end- stage renal failure.

Apart in periods of acute syndrome, SCD patients are ambulatory. The main causes of hospitalisation and death in patients with SCD are severe recurrent infections and subsequent complications such as vaso-occlusive crises. Average life-expectancy is 42 years in males and 48 years in females.

Hydroxycarbamide is a cytostatic myelosuppressive drug that, in most individuals, reactivates Fœtal Haemoglobin (HbF) synthesis. It has been marketed since 1968, in several EU member states, under different trade marks (Hydrea®, Litalir®, Oncocarbide®), for the treatment of haematological cancer and chronic myeloproliferative disorders, as polycythaemia vera and essential thrombocythaemia.

Considering SCD, hydroxycarbamide is the only product which efficacy has been studied in a relatively large placebo-controlled trial. Hydroxycarbamide appears, when used as monotherapy, to be the least toxic and most effective therapeutic option for SCD: hydroxycarbamide has been demonstrated to decrease the frequency of acute painful episodes, the incidence of acute chest syndrome, the

blood transfusion requirement and morbidity and mortality[5,6]. However, hydroxycarbamide therapy is not effective in all patients. Children are usually good responders, but it is estimated that 10 to 25% of adult patients are refractory to this therapy due to hypoplastic bone marrow, genetic factors, or variations in drug metabolism. Furthermore, significant variation of HbF production is observed in good responder patients[7,8].

In summary, SCD is one of the most common inherited diseases worldwide. It is associated with lifelong morbidity and a reduced life expectancy, and any evaluation of the safety profile of treatments for SCS must take into account the significant morbidity and mortality associated with the disease, independent of treatment.

It is estimated that between 400 and 500 patients are chronically treated by Hydrea® in France. This represents a significant part of the severe SCD patients.

Although the role of hydroxycarbamide in the prevention of painful crises and in the decrease of mortality and morbidity in SCD patients is well-established [5,9,10], long-term safety data with hydroxycarbamide in this indication is limited, particularly in certain sub-populations :

- Young patients
- Patients with hepatic or renal impairment
- During pregnancy or lactation
- Elderly patients.

The assessment of the leukemogenic potential of hydroxycarbamide is confounded by such observations being previously made in patients with underlying myeloproliferative diseases (*e.g.,* Essential Thrombocytemia and Polycytemia Vera).

Other concerns should be investigated:

- Concomitant use of hydroxycarbamide and HIV drugs
- Concomitant use of hydroxycarbamide with myelopsuppressive agents and radiation therapy.
- Concomitant use of live vaccines.

Siklos® is an orphan product. It is the only hydroxycarbamide authorised in SCD treatment. It is indicated for the prevention of recurrent painful vaso-occlusive crises including acute chest syndrome in both children and adult patients. Unanswered questions remain about its long-term safety especially in young patients who might be exposed for decades.

In order to answer all these questions, the European Medicine Agency (EMA) requested for a European cohort study to be performed. The present study will be performed to respond to this EMA demand. It aims to explore and collect information about the effects of Siklos® and its long-term safety in SCD patients.

2 Objectives

This study is driven by the Risk Management Plan required by EMA.

The objective of this cohort study is to collect information about long-term safety of Siklos® (hydroxycarbamide) when used in current practice for the prevention or treatment of symptomatic complications in patients with Sickle Cell Disease, assessed on the frequency of :

- Myelosuppression (requiring permanent or temporary discontinuation of therapy) secondary to hydroxycarbamide-induced myelotoxicity
- Malignancies, skin ulceration and impaired postnatal development (growth)
- Amenorrhea, fertility impairment.

Particular attention will be given to special populations or circumstances:

- Young patients (children and adolescents until end of puberty)
- Elderly patients
- Patients with underlying SCD-related hepatic or renal impairment
- Pregnancy and its outcome, particularly for congenital malformations
- Concomitant use of hydroxycarbamide and specific therapies :
  - HIV drugs ; especially Nucleoside Analogue Reverse Transcriptase Inhibitors (NRTI)
  - other myelosuppressive agents
  - radiation therapy
  - live vaccines

Other points of concern are:

- Overall mortality and survival time
- Occurrence of SCD events, in particular :
  - painful crises
  - infectionsacute chest syndrome
  - stroke
  - acute splenic sequestration

3 Investigational plan

This is a multicentre, prospective, non-interventional cohort study in patients with SCD treated with Siklos® and followed-up for up to ten years. Patients will be initially recruited in France, United-Kingdom and Greece. The other European countries will be encouraged to participate as soon as Siklos® becomes available.

All patients prescribed Siklos® within 8 years of its commercialisation until reaching at least 2000 patients will be enrolled in this cohort.

The follow-up of these patients will be strictly observational and will fit within their usual clinical monitoring without any controlled treatment, specific exam or modification of their follow-up, in compliance with the SPC of this orphan product.

Patients will be evaluated at inclusion, then every 1 to 4 months, according to normal monitoring of the disease and to the recommendations of Siklos® specification for use. A minimum of a yearly follow-up will be requested.

Patients will be informed by their initiating physician about the study and enrolled in case they agree to participate. Solely physicians experienced in the care of SCD (reference centres) are legitimated to initiate a Siklos® treatment; follow-up is authorised by both initiating and treating physicians. Patients will give their agreement for the retrospective collection of their data since Siklos initiation. This is justified by the fact that the initiation period is a sensitive period for potential adverse events.

A Steering Committee, formed by medical experts from all the countries involved in the cohort, sponsor representatives and an independent epidemiologist, will oversee the conduct and reporting of the cohort, to assure expert clinical guidance and a high standard of scientific quality.

A Clinical Board committee, formed by at least one physician expert in SCD management in each participating country, will animate the cohort follow-up in each country and ensure its development, and will propose actions to the Steering Committee.

CROs are appointed by the sponsor to ensure the study management: enrolment of participating physicians, study monitoring, data collection through electronic forms (e-CRF), data management, statistics and reporting to the Steering Committee.

Analyses of data collected will be conducted at least twice a year, to fit with the Risk Management Plan and Periodic Safety Update Reports.

4 Cohort Population

The cohort is composed of patients suffering from symptomatic SCD and entitled to a treatment with Siklos®.

4.1 Number and type of patients

Around 2000 patients treated with Siklos®.

The number of subjects is determined taking into account 20% of severe SCD on an overall 24 000 estimated number of subjects with the disease in Europe, and approximately 50% of these on Siklos®.

4.2 Recruitment criteria

Patients will be enrolled in the study cohort if they satisfy the following criteria

- Male or female ambulatory patients
- Aged 2 years and more
- With symptomatic sickle cell syndrome
- Treated with Siklos®
- Having been informed of the study by the initiating physician and consenting to participate to the cohort (for children, the persons having parental authority must be informed and give a participation consent)

4.3 Patients identification

A unique identifying number will be generated automatically based on the position of the subject in the cohort, on four digits with a one digit key-control added to the four digits number.

Additional information is collected for the physician convenience:

- Patient's date of birth.

5 Treatment

The dosage should be based on the patient's body weight.

The starting dose of Siklos® is 15 mg/kg/day and the usual dose is between 15 and 30 mg/kg/day. Under exceptional circumstances a maximum dose of 35 mg/kg/day might be justified under close haematological monitoring.

Duration: As long as the patient responds to therapy either clinically or haematologically (*e.g.*, increase of Haemoglobin F (HbF), Mean Corpuscular Volume (MCV), neutrophile count) the dose of Siklos® should be maintained.

In case of non-response (re-occurrence of complications or no decrease in complication rate) the daily dose may be increased by steps of 5 mg/kg/day.

In the event a patient does still not respond when treated with the maximum dose of hydroxycarbamide (35 mg/kg/day) over three to six months, permanent discontinuation of Siklos® should be considered.

The initial prescription of Siklos® must be done by a physician experienced in SCD management (initiating physician), normally a hospital physician. Renewing of prescription can be done by the treating physician, providing an annual renewal of prescription is done by the initiating physician.

6 Evaluation Criteria

6.1 Safety parameters

The primary safety parameters will be :

- Frequency of malignancies
- Frequency of skin ulceration (broken out by severity)
- Frequency of myelosuppression requiring temporary or permanent discontinuation of Siklos®.

The secondary safety parameters will be :

- Effects of Siklos® on growth development. Specific examinations (scintigraphy, radiographies, …) should be done if the difference with normal growth is greater than 2 standard deviations
- Outcome of pregnancies: rates of miscarriage, stillbirths, APGAR score at birth, congenital malformations.
- Frequency of serious adverse events.
- Any occurrence of unforeseen safety patterns.

Special attention will be given to specific populations or conditions, *e.g.*: elderly patients, patients with renal and hepatic impairment, HIV patients, patients receiving live vaccine or other myelosuppressive agents or radiotherapy, …

Definitions for AEs, SAEs and pregnancies, as well as procedures to follow are presented in Section 7. It is of utmost importance that all people participating in the trial understand these definitions and procedures. It is the investigator's responsibility to ensure that this knowledge is acquired.

6.2 Parameters assessing Siklos® effects

The effects on Siklos® on SCD will be assessed on the following non limitative list :

- Overall mortality and survival rates
- Frequency of vaso-occlusive complications :
  - painful crises
  - acute chest syndrome
  - stroke
  - acute splenic sequestration
  - infections
- Hospitalisations due to SCD events
- Frequency of blood transfusions

7 Adverse Event Reporting

7.1 Definitions

7.1.1 Adverse Event

An adverse event is any untoward medical occurrence in a subject taking Siklos®; the event need not necessarily have a causal relationship with the treatment or usage. Examples of adverse events include but are not limited to :

- Abnormal test findings
- Clinically significant symptoms and signs
- Changes in physical examination findings
- Hypersensitivity
- Progression/worsening of underlying disease.

Additionally, they may include signs or symptoms resulting from :

- Drug overdose
- Drug withdrawal
- Drug abuse
- Drug misuse
- Drug interactions
- Drug dependency
- Exposure in utero
- Pregnancy and lactation.

7.1.2 Serious Adverse Events

A serious adverse event or serious adverse drug reaction is any untoward medical occurrence at any dose that :

- Results in death
- Is life-threatening (immediate risk of death)
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Results in congenital anomaly/birth defect.

Medical and scientific judgement should be exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalisation. However, if it is determined that the event may jeopardise the subject and/or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse.

7.1.3 Adverse Reaction

An adverse reaction is defined as a response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function.

Response in this context means that a causal relationship between Siklos® and an adverse event is at least a reasonable possibility. Adverse reaction also includes adverse clinical consequences associated with use of the product outside the terms of the Summary of Product Characteristics or other conditions laid down for the marketing and use of the product (including prescribed doses higher than those recommended, overdoses or abuse).

7.1.4 Unexpected Adverse Reaction

An unexpected adverse reaction is an adverse reaction which nature, severity or outcome is not consistent with the Summary of Product Characteristics (SmPC). This includes class-related reactions mentioned in the SmPC but not specifically described as occurring with this product.

7.1.5 Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event are as follows :

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in Siklos® dosing based on SmPC recommendations or discontinuation from ESCORT-HU, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an adverse event by the physician or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an adverse event. Any abnormal test result that is determined to be an error does not require reporting as an adverse event.

7.1.6 Hospitalisation

Hospitalisation for worsening of a pre-existing condition (*e.g.*, for work-up of persistent pre-treatment lab abnormality) or any event related to sickle cell disease should be considered as a serious adverse event.

Hospitalisation or prolongation of hospitalisation in the absence of a precipitating, clinical adverse event is not in itself a serious adverse event and should not be reported. Examples include :

- Admission for treatment of a preexisting condition (except sickle cell disease) not associated with the development of a new adverse event
- Social admission (*e.g.*, subject has no place to sleep)
- Administrative admission *(e.g.,* for yearly physical exam)
- Optional admission not associated with a precipitating clinical adverse event (*e.g.*, for elective cosmetic surgery)

- Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as adverse events. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an adverse event. For example, an acute appendicitis that begins during the adverse event reporting period should be reported as the adverse event, and the resulting appendectomy should be recorded as treatment of the adverse event.

7.1.7 Exposure In Utero

Amendment 1 : *Despite specific recommendations regarding necessity to use contraception while taking Siklos (Summary Product Characteristics), despite specific recommendations regarding patient desire of pregnancy, indicating that Siklos has to be stopped 3 to 6 months before conception, an exposure to Siklos in-utero can occurs. According to the needs detailed in the Risk Management Plan (mod 1.8 Rev 4 page: 41 and 47) to follow specifically all pregnancies in the frame of Escort-HU, the following procedure has to be set up.*

An exposure in-utero (EIU) occurs if :

- A female becomes, or is found to be, pregnant either while receiving or having been directly exposed to Siklos® (*e.g.*, environmental exposure), or the female becomes, or is found to be, pregnant after discontinuing and/or being directly exposed to Siklos® (maternal exposure)
- A male has been exposed, either due to treatment or environmental, to Siklos® prior to or around the time of conception and/or is exposed during the partner pregnancy (paternal exposure).

If any subject or subject's partner becomes or is found to be pregnant during the subject's treatment with Siklos®, the physician must submit this information to Addmedica on an Exposure in Utero Form. In addition, the physician must submit information regarding environmental exposure to a Addmedica product in a pregnant woman (*e.g,.* a nurse reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the Exposure in Utero Form. This must be done irrespective of whether an adverse event has occurred and within 24 hours of awareness of the pregnancy. The information submitted should include the anticipated date of delivery (see below for information related to induced termination of pregnancy).

Follow-up is conducted to obtain pregnancy outcome information on all Exposure in Utero reports with an unknown outcome. The physician will follow the pregnancy until completion or until pregnancy termination (*i.e.*, induced abortion) and then notify Addmedica of the outcome. The physician will provide this information as a follow up to the initial Exposure in Utero Form. The reason(s) for an induced abortion should be specified. An EIU report is not created when an ectopic pregnancy report is received since this pregnancy is not usually viable. Rather, a serious adverse event case is created with the event of ectopic pregnancy.

If the pregnancy outcome meets the criteria for immediate classification as a serious adverse event *i.e.*, spontaneous abortion (including miscarriage and missed abortion), stillbirth, neonatal death, or congenital anomaly (including that

in an aborted foetus, stillbirth or neonatal death), the physician should follow the procedures for reporting serious adverse events.

In the case of a live birth, the "normality" of the newborn can be assessed at the time of birth (*i.e.,* no minimum follow-up period of a presumably normal infant is required before an Exposure in Utero Form can be completed). The "normality" of an aborted foetus can be assessed by gross visual inspection, unless pre- abortion test findings are suggestive of a congenital anomaly.

All neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as serious adverse events. In addition, any infant death after 1 month that the physician assesses as possibly related to the in utero exposure to the investigational medication should be reported.

All births (normal or not) will be followed on the long term by questioning the mother or the father (the subject having taken Siklos®) on follow-up visits. In case of adverse event which is assessed by the physician as related to mother's or father's administration, it will be managed upon post-MAA pharmacovigilance rules.

7.2 Reporting Adverse Events

All observed or volunteered adverse events regardless of suspected causal relationship to Siklos® will be reported as described in the following sections.

The physician is to report all directly observed adverse events and all adverse events spontaneously reported by the subject on the adverse event page(s) of the database. In addition, each subject will be questioned about adverse events.

For all adverse events not related to sickle cell disease, the physician must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event requiring immediate notification to Addmedica or its designated representative. For all adverse events not related to sickle cell disease, sufficient information should be obtained by the physician to determine the causality of the adverse event. The physician is required to assess causality. For adverse events not related to sickle cell disease with a causal relationship to Siklos®, follow-up by the physician is required until the event or its sequelae resolve or stabilise at a level acceptable to the physician, and Addmedica concurs with that assessment.

Each adverse event not related to sickle cell disease is to be assessed to determine if it meets the criteria for serious adverse event. If a serious adverse event occurs, expedited reporting will follow local and international regulations, as appropriate.

7.2.1 Reporting Period

Serious adverse events require immediate notification to Addmedica or its designated representative, beginning from the time that the subject provides oral informed consent to participate in a cohort follow-up called ESCORT-HU, *i.e.*,

prior to receiving Siklos®, through and including 28 calendar days after the last administration of Siklos®. Any serious adverse event occurring any time after the reporting period must be promptly reported if a causal relationship to Siklos® is suspected.

Adverse events (serious and non-serious) should be recorded in the database from the time the subject has taken at least one dose of Siklos® through 28 calendar days after the last administration of Siklos®.

7.2.2 Severity Assessment

If required on the adverse event case report forms, the physician will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the adverse event. For purposes of consistency, these intensity grades are defined as follows :

MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

Note the distinction between the severity and the seriousness of an adverse event. A severe event is not necessarily a serious event. For example, a headache may be severe (interferes significantly with subject's usual function) but would not be classified as serious unless it met one of the criteria for serious adverse events, listed above.

7.2.3 Causality Assessment

The physician's assessment of causality must be provided for all adverse events not related to sickle cell disease (serious and non-serious). A physician's causality assessment is the determination of whether there exists a reasonable possibility that Siklos® caused or contributed to an adverse event. If the physician's final determination of causality is unknown and the physician does not know whether or not Siklos® caused the event, then the event will be handled as "related Siklos®" for reporting purposes. If the physician's causality assessment is "unknown but not related to Siklos®", this should be clearly documented on study records.

7.2.4 Serious Adverse Event Reporting Requirements

If a serious adverse event occurs, Addmedica is to be notified within 24 hours of awareness of the event by the physician. In particular, if the serious adverse event is fatal or life-threatening, notification to Addmedica must be made immediately, irrespective of the extent of available adverse event information. This timeframe also applies to additional new information (follow-up) on previously forwarded serious adverse event reports as well as to the initial and follow-up reporting of Exposure in Utero cases.

In the rare event that the physician does not become aware of the occurrence of a serious adverse event immediately (*e.g.*, if an outpatient subject initially seeks treatment elsewhere), the physician is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the adverse event.

For all serious adverse events, the physician is obligated to pursue and provide information to Addmedica in accordance with the timeframes for reporting specified above. In addition, a physician may be requested by Addmedica to obtain specific additional follow-up information in an expedited fashion. This information may be more detailed than that captured on the adverse event case report form. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Addmedica or its designated representative.

8 Data collection

Data will be collected electronically in a database created and monitored by CROs.

During this study, patients can be followed-up by both the initiating and the treating physicians. Only the former is allowed to initiate Siklos® treatment and by the same way to enroll new patients in the study. Familial physician is allowed to access to data recorded by initiating physician and to record new data collected during the patient follow up visits.

8.1 Physician identification

Physicians (treating physicians or specialised physicians initiating Siklos® treatment) will be identified using the following informations :

- Username
- First name
- Last name
- Hospital Centre
  - Address
  - City
  - ZIP/Postal code
  - Country
- Phone
- E-Mail
- Title
- National physician number
- Speciality
- Current functions

8.2 Baseline data

Demographic characteristics : date of birth, gender, height, weight.

School, occupation.

History of SCD :

- Type of expressed Hb: HbSS, HbSC, HbSβ° or HbS β+. This data is assessed routinely in SCD and is necessary to determine its severity
- Whether the diagnosis was made as neonatal screening
- Date (or year) of first appearance of SCD symptoms
- Date (or year) of SCD diagnosis

- History of SCD manifestations :
  - history of growth delay
  - infections during the elapsed year
  - number and type of vaso-occlusive complications during the elapsed year :
    - painful crisis
    - acute chest syndrome
    - priapism
    - stroke
    - hepatopathy
    - acute splenic sequestration
    - other
  - Number of hospitalisation in relation with

    SCD. Presence or absence of skin

    ulceration.

Any history of malignancy (type, location, date, resolution).

In males whether sperm had been examined.

In females obstetric history (if applicable).

Treatment history data :
- Blood transfusions
- History of treatment by hydroxycarbamide (other than Siklos®) will be also documented: start, end dates, last dose.

Siklos® treatment initiation: date of treatment start, dosage. If the patient is not prescribed Siklos®, reason.

Other relevant concomitant conditions and associated treatment.

Clinical examination.

Biological data, as performed routinely in the disease management, with at least Haemoglobin, MCV, HbF, ferritin, white cell count and differential, platelets, urinalysis (protein), liver function tests, blood urea and creatinine.

8.3 Follow up form

Demographic data : height, weight.

Growth, school, occupation.

Presence or absence of skin ulceration

Malignancy (type, location, date, resolution).

Pregnancy (see below).

Other concomitant pathologies/adverse events with description, seriousness, start and end date, outcome, severity, relation with a pre-existing condition, ancillary examination, and relationship to Siklos®

Concomitant treatments, in particular :
- HIV drugs (NRTI)
- Myelosuppressive agents
- Radiotherapy
- Live vaccines

Infections.

Number and type of vaso-occlusive complications :
- Painful crisis
- Acute chest syndrome
- Priapism
- Stroke
- Hepatopathy
- Acute splenic sequestration
- Other

Number of hospitalisation in relation with SCD.

Number of transfusions.

Clinical examination.

Biological data : at least blood count, liver function tests, blood urea and creatinine.

Siklos® information: changes in dosage, temporary discontinuations, withdrawal of treatment and reasons.

8.4 Withdrawal form

- Date of last information available.
- Reasons for discontinuation.

8.5 Pregnancy form

If any subject is found to be pregnant during the treatment follow-up, the evaluation of the risk-benefit ratio will be made on an individual basis outweighing the respective risk of continuing Siklos® therapy against the switch to a blood transfusion programme. Siklos® should normally be stopped.

The pregnancy should be reported immediately using the pregnancy notification form available in the database.

All pregnancies will be followed up to final outcome, using the pregnancy follow-up form. The outcome, including any premature termination, miscarriage or foetal death will be reported.

The follow-up of children born from a parent receiving Siklos® is a Pharmacovigilance concern. Such children will be followed-up for at least one year.

8.6 Collection of AEs and SAEs

Adverse events, serious or not, will be collected in a specific form available in the database. These effects will be reported according to the ADDMEDICA Pharmacovigilance SOPs.

For all the AEs not related to sickle cell disease recorded, will be collected information about:

- Description, serious or not
- Start date
- Outcome
- End date (if applicable)
- Severity
- Relation with previous pathology
- Ancillary Examination
- Corrective treatment
- Relationship to Siklos® (suspected / not suspected)

For all the events related to sickle cell disease recorded, will be collected information about:

- Start date
- Outcome
- End date (if applicable)
- Severity
- New Transcranial Doppler done or not

8.7 Data protection

Data encryption

In order to respect patient anonymity, in the database, all personal data allowing patient identification will be encrypted.

Rights of access

Physician selected to perform the study and the CRO personal implicated in the study conduction are allowed to access to this database. Addmedica and competent authorities are allowed to access to data recorded in case of audit. For each authorised person, a login and a password will be created. All these persons have a duty of confidentiality to the patients and will do their best to meet this duty.

NB: In the database all passwords (used by users or administrators) will be encrypted.

9 Recruitment and follow-up

9.1 Recruitment of physicians specialised in SCD

In each country an exhaustive list of all treatment centres specialized in SCD or haemoglobinopaties care (haematologists, paediatricians, internist…) will be established in collaboration with the Steering Committee (SC) and the European Clinical Board Committee (ECBC) (See section 7).

Furthermore, with the physicians profile defined in each country the study sponsor will consider availability of any specific physicians database.

A mailing will be sent to the full list of identified physicians to inform, propose and motivate them to participate in this study. In case of agreement, the CRO will contact each of them to explain the study and to set up a secure access to the database.

9.2 Recruitment of patients and follow-up

Patients fulfilling all the inclusion criteria will be informed by their initiating physician about the study and enrolled in case they agree to participate. It is noteworthy that solely the physicians specialised in the care of SCD are legitimated to initiate a Siklos® treatment. However, the follow-up is authorised by both initiating and treating physicians.

9.3 Study conduction

For each patient initiated by SIKLOS®, the initiating physician will fill the information on the current treating physician in the database. In case of this physician is unknown in the study database, the CRO will contact him to propose to participate in the study.

A Family Doctor Pack (treating physician pack) written in local language will be sent to the treating physician for treatment information and follow-up purpose (monitoring of blood count, dosage adjustment, pregnancy, AEs). The details of the cohort study will be included in this pack. The treating doctors will be invited to complete an electronic form at each visit (intermediate visit form) so that any adverse effects can be followed up in a timely manner.

Patients will be followed-up according to normal local medical practice. Each treating physician will be included in the database and a reminder will be send regularly (4 months) in case of non follow-up data capture for a patient.

Once a year, a follow-up should be mandatory.

Furthermore a patient card will be provided to the patient so that, in case of events (hospitalisations, intercurrent events, adverse events…) any physician would be able to contact the CRO.

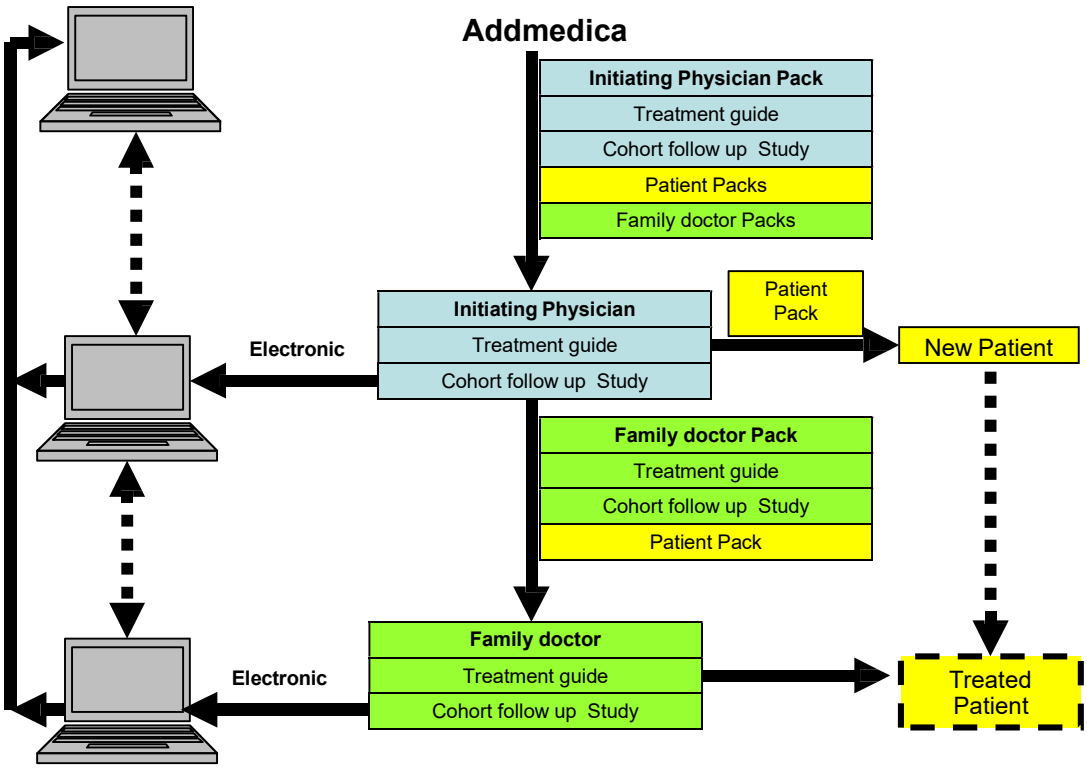
If no forms are received for a year, the patient will be considered as having been withdrawn from the study. In this case, a specific withdrawal form will be

completed if it is possible, patients who discontinue Siklos® will continue to be monitored until the end of the study (10 years).

9.4 Flow chart

The cohort follow-up is illustrated in the flow chart presented below.

The forms will be completed electronically in the database.



10 Monitoring

Quality control visits will be performed to verify data entered in the Case Report Form against patient medical files.

11 Management and validation of data

The CRO (Arone) is responsible for management of collected data (construction of a Database) and their validation.

Data will be collected on Electronic Case report Form.

It is the responsibility of the participating physicians :

- To obtain subject data and collect them in a prospective manner by questioning the patient; some data could be collected retrospectively in patients when enrolment in posterior to initiation of treatment by Siklos
- To ensure that all data collected are recorded directly, accurately and legibly
- To perform the requested measurements.

100% of at least 5% of visits will be controlled.

The first on-site quality control visit will be triggered after the inclusion of the fifth patient at a site (i.e. patient visits available in eCRF with at least the first year of follow-up for one of the patient that means 3 visits). After the first on-site visit, only the biggest recruiting sites will be visited yearly (defined with the sponsor, based on the number of patients included).

Qualified designated personnel will perform this quality control in each country.

All study related material will be archived securely according to relevant internal procedures.

A detailed archiving procedure will ensure that access to confidential information is limited and that the confidentiality of information about study subjects is protected.

The archives should be maintained for at least five years after final report or first publication of study results, whichever come first.

12 Analysis and Reports

All statistical analyses will be performed at the 5% significance.

Parameters will be summarised using mean, median, standard deviation, range for continuous data and counts or percentages for categorical data.

Descriptive statistics will be used to:
- Report the prevalence of primary and secondary parameters
- Describe the global population and the sub-populations.

Appropriate multivariate analysis will be used to describe the determinants of the observed events.

Regular interim reports will be issued in accordance with the PSUR schedule.

The report will present a general description of the population included and frequencies of all primary and secondary parameters on the global population.

Sub-population analyses will be performed when the collected data on the same parameters will be sufficient.

The following formula is used to calculate the confidence interval of a given frequency estimate p.

$$\left[p - z_{1-\alpha/2}\sqrt{\frac{p(1-p)}{N}}; p + z_{1-\alpha/2}\sqrt{\frac{p(1-p)}{N}} \right]$$

with $z_{1-\alpha/2}$ the $1-\alpha/2$-quantile of the standard normal distribution (=1.96), α=5% the significance level and N the sample size. The quantity $z_{1-\alpha/2}\sqrt{\frac{p(1-p)}{N}}$ can be seen as the precision of the estimate p.

The expected sample size of N=2,000 patients will allow the following precision on frequency estimates p:

Frequency p	Precision	95% confidence interval
0,05	0.0096	[0.0404 ; 0.0596]
0,01	0.0044	[0.0056 ; 0.0144]
0,005	0.0031	[0.0019 ; 0.0081]

13 Committees

13.1 European Clinical Board Committees (ECBC)

In each European country involved in this study, a clinical board committee including physicians will take place. The missions of these committees are the following :

- To animate the cohort follow-up in each country and ensure its development
- To propose and decide on development of the action to set up.

A European Clinical Board Committee charter will define more precisely the responsibilities of these committees.

13.2 Steering Committee (SC)

A Steering Committee will comprise the physician heading each of the European committees previously described, the sponsor, and an independent statistician. The Steering Committee will oversee the conduct and reporting of the cohort follow-up, assuring expert clinical guidance and a high standard of scientific quality, reviewing all SAEs and clinical endpoints reported by the sites (*i.e.*, initial diagnoses, laboratory values, results of procedures) to determine the occurrence of clinical issues and proposing any necessary protocol amendments to be submitted to the competent authorities.

Members of the committee will be determined according to their skills,

number of patients included in their center, availabilities for meeting

and interest in participating.

14 Legal framework and patient information

14.1 Legal framework

As previously described, this study will be conducted to respond to EMA demand. It will consist in data collection and will not involve any change in the usual patient follow-up. Thus, patients must agree to participate (either orally, or by writing according to local regulations). Anyway, patients (or their legal guardians) will be informed orally about the study by their physician and will be given a written information sheet. All measures will be taken to guarantee the anonymity and the confidentiality of personal data.

Authorisations to perform the study will be requested from each local authority as required in accordance with the local regulation.

14.2 Description of the patient information sheet

Oral information will include objectives of the study, nature, addresses and duration of preservation right of the data, the conditions of access rights and of rectification as well as the right to opt out. These information will also be provided as a written note to every patient (or persons having parental authority) before the transmission of any data. Date of its delivery will be reported in the data collection forms.

15 References

1 Pearson HA et al. Functional asplenia in sickle-cell anemia. N Engl J Med. 1969; 281:923-926.

2 Wigfall DR et al. Prevalence and clinical correlates of glomerulopathy in children with sickle cell disease. J Pediatr. 2000; 136:749-753.

3 Powars D et al. Sickle cell chronic lung disease: prior morbidity and the risk of pulmonary failure. Medicine (Baltimore). 1988; 67:66-76.

4 Pegelow CH et al. Longitudinal changes in brain magnetic resonance imaging findings in children with sickle cell disease. Blood. 2002; 99:3014-3018.

5 Charache S et al. Effect of hydroxyurea on the frequency of painful crisis in sickle cell anemia. Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia. N Engl J Med. 1995; 332:1317-1322.

6 Lı ´gia Barbosa Braga et al. Hemoglobin, 29 (3):171-180. (2005)

7 De Montalembert et al. J Pediatr Hematol Oncol. 1997; 19 (4):313-8

8 Maier-Redelsperger et al. Blood. 1998; 91 (12):4472-9

9 Platt OS et al. Mortality in sickle cell disease: life expectancy and risk fac-tors for early death. N Engl J Med. 1994; 330:1639-1644.

10 Thomas AN et al. Causes of death in sickle cell disease in Jamaica. Br Med J (Clin Res Ed). 1982; 285:633-635.

Appendices

Responsibilities of the Marketing Authorisation Holder

In the context of the European Risk Management Plan, the Agency (EMA) requests to Addmedica to initiate a cohort follow-up. This cohort follow-up, a post-authorisation safety study, was carried out in accordance with the terms of marketing authorisation, and should be conducted with the aim of identifying or qualifying a safety hazard relating to Siklos®.

Addmedica is the Marketing Authorisation Holder (MAH) of Silkos®. AnticipSanté is responsible on behalf of the MAH, for managing and reporting pharmacovigilance activities to the concerned Competent Authorities (EMA, local health authority). Peter Holmes Clinical is responsible for providing and maintaining the electronic case report form, including serious adverse events forms.

The legal framework for pharmacovigilance of medicinal products for human use in the European Union (EU) is given in Regulation (EC) No 726/20041 and Directive 2001/83/EC2 on the Community code relating to medicinal products for human use, as last amended by Directive 2004/24/EC3 and by Directive 2004/27/EC4 (hereafter referred to simply as Directive 2001/83/EC). It should be noted that although Chapter 3 of Regulation (EC) No 726/2004 and Title IX of Directive 2001/83/EC contain the majority of pharmacovigilance provisions in the legislation, other measures directly relevant to the conduct of pharmacovigilance are found in other Chapters and Titles of those legislative texts.

The requirements explained in these guidelines are based on the ICH guidelines, where these exist, but may be further specified or contain additional requests in line with the legislation of the EU.

Responsibilities for the Conduct of Post-Authorisation Safety Studies

The Marketing Authorisation Holder who initiates, manages and/or finances the cohort follow-up is responsible for its conduct and should meet the pharmacovigilance obligations concerning PASS. The study should be supervised by a designated monitor(s) or monitoring organisation and the names of the monitors should be recorded in the study documents. In case the Marketing Authorisation Holder does not directly conduct the study, detailed and clear contractual agreements for meeting pharmacovigilance obligations should be documented.

The QPPV at EU level and/or, where applicable, the nominated person responsible for pharmacovigilance at national level, should be involved in the review of protocols for all post-authorisation safety studies, in order to ensure compliance with pharmacovigilance requirements.

Reports from Organised Data Collection Systems

Reporting requirements for cases derived from organised data collection systems (which include clinical trials, post-authorisation studies, registries, post-authorisation named-patient use programmes, other patient support and disease management programmes, surveys of Patients or Healthcare Providers, and

information gathering on efficacy or patient compliance) differ depending on whether they are derived from interventional or non-interventional studies.

Post-authorisation studies that are non-interventional are not covered by the provisions of Directive 2001/20/EC but by Directive 2001/83/EC and Regulation (EC) No. 726/2004 (see Annex 1.1 for the definition of a non-interventional trial). Serious adverse reactions arising from such studies should be reported on an expedited basis according to the same criteria and timelines as adverse reactions reported spontaneously by Healthcare Professionals (see Chapter I.4, Section 1); this includes any suspected transmission via a medicinal product of an infectious agent. For an overview on the expedited reporting requirements in Member States, see Annexes 6.1.1, 6.1.2 and 6.1.3. All adverse reactions, i.e. also non- serious ones, should be included in the final study report. For reporting of adverse reactions in the Periodic Safety Update Reports (PSURs), see Chapter I.6. For further information on post-authorisation safety studies see Chapter I.7.

Reporting of Adverse Reactions

For non-interventional post-authorisation safety studies, conducted inside and outside the EU, the usual regulatory requirements for reporting of adverse reactions should be fulfilled.

This means that :

- Reports of all serious adverse reactions arising from such studies within the EU should be reported on an expedited basis (i.e. within 15 days), to the Competent Authority of the Member State on whose territory the incident occurred, and in addition, for products authorised through the mutual recognition or decentralised procedures and for products which have been the subject of a referral procedure, to the Reference Member State. These reports should also be included in the PSURs
- Reports of all unexpected serious adverse reactions arising from such studies outside the EU should be reported on an expedited basis to the Agency and to all Member States where the medicinal product is authorised. These reports should also be included in the PSURs
- Reports on expected serious occurring outside the EU should be reported in 6 on PSURs; all adverse reactions/events including those which are considered non-serious, should be summarized in the final study report in frequency tables.

Marketing Authorisation Holders should ensure that they are notified by the physician of serious adverse reactions and, if specified in the study protocol, of events (those not suspected by the physician or the Marketing Authorisation Holder to be adverse reactions).