PREGNANCY REGISTRY FOR EURARTESIM™

Study protocol
Protocol N° 3351

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CLINICAL ADVISORY BOARD

The role of the clinical advisory board is:

- to validate the objectives and methodology of the study
- to participate in creating the protocol, the study questionnaires and/or the study analysis and publication plans
- to review the results and analyses reports

A clinical advisory board (CAB) to the Pregnancy Registry for Eurartesim™ will be recruited from HCPs participating in the Registry and specialists in teratology, with changing participation over time. Initially, this CAB will be constituted by select local country Key Opinion Leaders (KOLs) who will act as a scientific advisory board to review and provide guidance on the study procedures. After initiation of the study, this group will meet annually to provide guidance on study conduct and review the study results to date.

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1. List of Abbreviations

ACT	Artemisinin-based Combination Therapy
AE	Adverse Events
BMI	Body Mass Index
CAB	Clinical Advisory Board
CDISC	Clinical Data Interchange Standards Consortium
COF	Contact Order Form
CRA	Clinical Research Associate
CRF	Case Report Form
DHA	Dihydroartemisinin
DSS	Demographic Surveillance System
EC	Ethics Committee
EMA	European Medicines Agency
ENTIS	European Network of Teratology Information Services
ERA	Epidemiologic Research Associate
EUROCAT	European Surveillance Network of Congenital Anomalies
EUROCRAN	European Collaboration of Craniofacial Anomalies
GP	General Practitioner

HCP	Healthcare Provider
KOL	Key Opinion Leader
MedDRA	Medical Dictionary for Regulatory Activities
MMV	Medicines for Malaria Venture
OB/GYN	Obstetrician/Gynaecologist
PQP	Piperaquine
R-M EU	REGISTRAT-MAPI Europe
SAE	Serious Adverse Events

2. Summary

Title of the study	Pregnancy Registry for Eurartesim™
Study design	A European multi-centre pregnancy Registry for patients exposed to Eurartesim™ whilst pregnant.
Study objectives	- The primary objective of this study is to assess the live birth incidence of minor and major congenital birth defects following exposure to Eurartesim™ whilst pregnant or in the one (1) month (30 days) prior to conception. - The secondary objective of this study is to assess both maternal and fetal outcome following exposure to Eurartesim™ whilst pregnant or in the one (1) month (30 days) prior to conception.
Methodology	The Eurartesim™ Registry is open to enrolment for all women with malaria who have been exposed to Eurartesim™ whilst pregnant. Initially, HCPs known to treat and follow-up malaria patients will be invited to collaborate. A recruitment mail containing the study summary and a reply form will be sent to the HCPs. Non-respondent HCPs will be contacted by phone. Women who are not part of one of the selected sites will be able to contact their HCP who will contact Sigma-Tau on their behalf in order to be included in the Registry. In addition, all patients with pregnancies reported to the company as spontaneous events by HCPs will also be asked to participate in the Pregnancy Registry. The HCP will include all patients meeting the inclusion criteria and agreeing to take part in the Registry. During this recruitment phase, and for each patient, the HCP will: - Explain the Registry to the patient (in particular the objective of the Registry and its observational nature), give her a patient information sheet, a Consent Form and a Contact Order Form and ask the patient to read, fill in and sign them to confirm her agreement, - Fill in the enrolment CRF of the registry, - Send by fax or mail the completed Contact Order Form to the unit in charge of the patient follow-up. These agreements must be obtained for the recruitment and follow-up of

	both the mother and her infant. The biological father will also be requested to give consent for the release of data referring to him; if the mother consents to participate in the registry but the biological father doesn't, then the mother and her infant will still be included in the registry but no data will be collected on the biological father. For non-included patients meeting the selection criteria, the HCP will collect few data in a short form (patient log) of the Registry. During follow-up visits/contacts, the HCP will: - Fill in the follow-up CRF of the registry. Data collection for all patients will be performed at enrolment, 4 weeks post-enrolment, 4 weeks pre-delivery, at delivery and 6 weeks post-delivery. Infants will be assessed at 6 weeks, 14 weeks and 12 months.
Clinical advisory board	A clinical advisory board (CAB) to the Pregnancy Registry for Eurartesim™ will be recruited from HCPs participating in the Registry, with changing participation over time. Initially, this CAB will be constituted by select local country KOLs who will act as a scientific advisory board to review and provide guidance on the study procedures. After initiation of the study, this group will meet annually to provide guidance on study conduct and review the study results to date.
Sample size estimate	Data for this pregnancy registry will be regularly collected until the sample size of 376 patients required to detect a 2-fold or greater increase relative to the expected background rate of all birth defects and spontaneous abortions is reached. The Registry will be closed to new entries once this number of women with validated follow-up information has been reached and in agreement with the EMA. The following sample size is derived to detect a clinically significant difference (i.e. a >2x increase in the outcome of concern) relative to expected background rates. The assumed background risk of all reported birth defects is 23.719 per 1,000 births (EUROCAT, 2009) and the background rate of spontaneous abortion is 85.6 per 1,000 (Tata *et al*, 2005). Thus, assuming 80% power, 0.05 significance level (one-sided) and a loss to follow-up rate of 5%, we would require 376 pregnant women exposed to Eurartesim™ in order to be able to detect a 2-fold or greater increase in birth defects and a 1.5-fold or greater incidence in spontaneous abortions with a one-group test.

Number of HCPs Countries	A total of 57 sites, represented across Belgium, France, Germany, Italy, The Netherlands, Spain and the UK, will be enrolled in order to recruit 376 patients over 5 years. 7 European countries; Belgium, France, Germany, Italy, The Netherlands, Spain, UK
Selection criteria	**Inclusion Criteria:** The following patients will be included in the study: - Women; - who have received Eurartesim™ for malaria whilst pregnant, within one (1) month (30 days) before or at any time after conception, or - whose partner (the biological father) has received any formulation of Eurartesim™ for malaria within one (1) month (30 days) prior to conception (Committee for Medicinal Products for Human Use, 2005), and - who have been informed and agree to participate in this study. **Exclusion Criteria:** The following patients must not be included in the study: - Women who refuse to participate. - Women participating in a clinical trial at the time of inclusion in the study.
Data collection	The following data will be collected from the HCP: **HCP enrolment form:** - Specialty. - Years in practice. - Geographic location. - Institution type. - Number of pregnant malaria patients currently treating. **At enrolment visit:** - Date of the visit. - Socio-demographic characteristics of the mother (ethnicity [based on the standard definitions of ethnicity used in the EU country where the woman is enrolled in the Registry], country

	of birth, primary language and socio-economic status [based on current or most recent occupation and years of formal education]). - Socio-demographic characteristics of the biological father (age and current or most recent occupation). - Mother's lifestyle data (height [cm] and weight [kg], radiation exposure, smoking status [never/past/current], alcohol consumption [weekly units], recreational drug use. - Mother's malaria history (date of malaria diagnosis, date of most recent Eurartesim™ administration and dose, previous Eurartesim™ administrations, other treatment taken for malaria). - Pregnancy data (date the pregnancy was registered). - Estimated date of delivery/date of last menstrual period. - Previous or concurrent maternal complications. - Health status of the fetus, if it is already known at time of enrolment, i.e. via ultrasound. - Pregnancy outcome, if already known at time of enrolment. - Obstetrical history (number of previous pregnancies and outcome). - Significant medical history of the mother and the biological father. - Concomitant medication use in the mother and the biological father in the one (1) month (30 days) prior to conception. **4-weeks post-enrolment and 4-weeks prior to expected due date:** - Date of the visit. - Serious adverse events (drug related or not) in the mother since previous visit/contact. - Exacerbation of pre-existent clinical condition in the mother since previous visit/contact.

	- Comorbidities in the mother since previous visit/contact. - Concomitant medication use in the mother since previous visit/contact. - Maternal complications since previous visit/contact. - Fetal complications since previous visit/contact; any spontaneous abortions (≤28 weeks gestation), elective abortions, ectopic pregnancies, late fetal or neonatal deaths (>20 weeks gestation), premature deliveries (≤37 completed weeks). **At end of pregnancy:** - Date of the end of pregnancy. - Maternal complications since previous visit/contact. - Maternal mortality. - Stillbirth (>28 weeks gestation). - Early neonatal mortality. - Gestational age at delivery (estimated from the last menstrual period). - Live births. - Infant birth weight (adjusted for gestational age). - Infant major and minor birth defects (primary outcome of interest). - Serious adverse events (drug related or not) in the mother or the infant since previous visit/contact. - Exacerbation of pre-existent clinical condition in the mother since previous visit/contact. - Comorbidities in the mother since previous visit/contact. - Concomitant medication use in the mother since previous visit/contact.

	6 weeks after end of pregnancy: - Date of the visit. - Maternal complications since previous visit/contact. - Maternal mortality. - Early neonatal mortality (≤7 days of birth). - Neonatal mortality (≤28 days of birth). - Infant major and minor birth defects. - Serious adverse events (drug related or not) in the mother or the infant since previous visit/contact. **14 weeks after end of pregnancy:** - Date of the visit. - Maternal complications since previous visit/contact. - Maternal mortality. - Infant mortality. - Serious adverse events (drug related or not) in the mother or the infant since previous visit/contact. - Infant development. **12 months after end of pregnancy:** - Date of the visit. - Serious adverse events (drug related or not) in the mother or the infant since previous visit/contact. - Infant development.
Statistical Analysis	Statistical analyses will be carried out using SAS software version 9.2. REGISTRAT-MAPI EU will prepare a statistical analysis plan to be reviewed by Sigma-Tau and the CAB. At regular intervals tables and listings will be produced to enable

reporting of key interim outcomes to regulatory authorities, participating HCPs and the scientific/medical community at large.

Reporting of data (other than individual reports concerning individual patients or participating HCPs to those individual participants), will be in aggregate form to ensure individual patient and HCP confidentiality.

All analyses, primary and secondary, will be conducted in two manners; on all women and by stratifying the women depending on whether they were directly exposed to Eurartesim™ or whether the biological father was exposed to Eurartesim™.

Primary analysis

In accordance with the primary objectives of the study and the way the study was powered, the main focus of the statistical analysis will be estimation of the incidences of birth defects and spontaneous abortion. 95% confidence intervals will be computed around these incidences in order to judge whether there is an increase of these incidences as compared to background risks.

In order to control for potential confounders, birth defects and spontaneous abortion will be described according to parameters such as concomitant infections/diseases and medication use.

For spontaneous abortions, women who discontinued the study prior to delivery will not be taken into account in the primary analysis. A sensitivity analysis will be performed considering all patients, assuming that women who discontinued the study prior to delivery had experienced spontaneous abortion; this will provide us with the highest estimation of incidence of spontaneous abortion (i.e. the worst-case scenario).

In the same way, in the primary analysis, incidences of birth defects will be analysed without considering patients who discontinued the study prior to 14 weeks after the end of pregnancy. A sensitivity analysis will be performed on all patients assuming that women who discontinued the study prior to 14 weeks after the end of pregnancy had experienced birth defects.

	Description of the study populations HCPs: HCPs will be described according to the data included in the HCP enrolment form. Tables and listings describing participating HCP characteristics will be produced (specialty, years in practice, geographic location, institution type, number of pregnant malaria (Registry) patients treated/site). Patients: Patients included in the study will be described according to demographic and background characteristics (e.g. age, ethnicity, duration and timing of exposure to Eurartesim™). **Pregnancy-related information** Frequency and type of pregnancy outcome will be stratified by the earliest trimester of exposure, demographics and medical background characteristics. Gestational weeks will be counted from the date of the last menstrual period, with the second trimester as beginning at week 14 and the third trimester as beginning at week 28. Women who discontinued the study prior to delivery will not be taken into account in the primary analysis. A sensitivity analysis of patients who did not complete the entire follow-up will be performed, in the same manner as described in the 'Primary analysis' section above. Time-to-event variables will be analysed via survival analysis methods (e.g. Kaplan-Meier survival estimates and associated confidence intervals). In order to control for potential confounders, pregnancy outcomes will be analysed according to parameters such as lifestyle factors, concomitant infections/diseases and medication use. Patient's Body Mass Index (BMI) will be calculated from the patient's height (cm) and weight (kg) data. In order to optimize patient recruitment, patients with recurring malaria and Eurartesim™ use during pregnancy will be included in this pregnancy Registry in addition to first malaria infections. However, first and

	recurring malaria infections will be analyzed separately due to the potential differences in disease aetiology and pregnancy outcomes. **Analytical methods** Continuous variables will be described by their mean, standard deviation, median, quartiles 1 and 3, extreme values (minimum and maximum) and the number of missing data. Categorical variables will be described by the total and percentage of each response method and the number of missing data. Continuous variables will be compared using Student's t-test (2 groups) or variance analysis (>2 groups). If the conditions for applying these tests are not met (normality, homoscedasticity), the Mann-Whitney, Wilcoxon (2 groups) or Kruskal-Wallis (>2 groups) non-parametric tests will be used. Categorical variables will be compared between subgroups using the Chi-2 test if the theoretical total of each class studied is greater than 5. Otherwise Fisher's exact test will be used. The ordinal variables will be compared between subgroups using a Cochran-Mantel-Haenszel test. Hypothesis formulation will be bilateral. The tests will be performed for a first species alpha risk of 5%.
Registry timelines	These timelines are based on Eurartesim™ being available on the market by June 2012: Validation of study documents: June 2012 Ethics submission: June 2012 Launch of Eurartesim™: June 2012 First patient in: July2012 Recruitment rate analyses: December 2012, every 1 year after Interim statistical analyses: June 2014, every 2 years after Last patient in: May 2017 Final Clinical Study Report: September 2019

3. Introduction and justification for the study

Currently, malaria is one of the leading killer diseases in the world. According to the newly released WHO Malaria Report 2008, "there were an estimated 247 million malaria cases among 3.3 billion people at risk in 2006 causing nearly a million deaths, mostly of children under 5 years. One hundred and nine countries were endemic for malaria in 2008, 45 within the African region".

Eurartesim™ (dihydroartemisinin (DHA) - piperaquine (PQP)) is an artemisinin-based combination therapy (ACT), which involves the simultaneous use of two or more blood schizontocidal medicines with independent modes of action and, thus, different biochemical targets in the parasite. The rationale is two-fold: i) the combination is often more effective; and ii) in the very rare event that a mutant parasite resistant to one of the medicines arises de novo during the course of the infection, this resistant parasite will be killed by the other antimalarial medicine. This mutual protection is thought to prevent or to delay the emergence of resistance and ACTs have replaced chloroquine in treating malaria because malaria parasites have become resistant to the old malaria drugs. To realize the two advantages, the partner medicines in a combination must independently be sufficiently efficacious in treating malaria (WHO, 2010).

The ACTs have undergone the three trial stages and pre-clinical data has demonstrated embryotoxicity (lethality and teratogenicity) with artemisinin compounds. Substantial data are available in patients for DHA-PQP combination treatment, including neurotoxicity of artemisinin derivatives, cardiotoxicity and QTc prolongation, and reproductive toxicity (i.e. DHA embryolethality in animals). Previous animal models have established that artemisinin derivatives, as well as DHA, have serious embryotoxigenicity in rat and rabbit embryos/foetuses (Sigma-Tau, 2009).

To date, some recent *in vitro* results on DHA studied in the rat whole embryo culture demonstrated that DHA primarily affected primitive red blood cells (Longo *et al*, 2006a; Longo *et al*, 2006b). Tissue damage and effects on embryo morphology were attributed to this. Despite the absence of maternal anaemia, yolk sac haematopoiesis was also seen as the target of DHA *in vivo*. Resulting anaemia leads to cell damage, which, depending on its degree, can be either diffuse or focal. Embryo response to acute anaemia varies from complete recovery to malformation and death depending on the degree of cell death induced.

In vivo studies (White *et al*, 2006) showed that four artemisinins (artesunate, DHA, artemether and arteether) administered orally to pregnant rats on day 10 post-coitum

caused nearly equivalent effects in terms of embryolethality and teratogenicity (cardiovascular defects and shortened and/or bent long bones). This, therefore, suggests that embryotoxicity is an artemisinin class effect (WHO, 2006). The developmental toxicity is thought to be dependent on the high sensitivity of embryonic erythroblasts to artemisinins compared to adult erythroblasts. Since decreases in reticulocyte count occur at therapeutic doses in humans following artemisinin treatment, there is concern that this could be accompanied by marked decreases in embryonic erythroblasts and developmental toxicity if artemisinin is administered during the first trimester of pregnancy. DHA affects human erythropoiesis *in vitro*, in a dose- and time-dependent manner; the target populations seem to be the pro-erythroblasts and basophilic erythroblasts, suggesting that DHA toxicity is limited to primitive human erythropoiesis.

In a further study, Rijken *et al* (2008) treated 50 pregnant women with recurrent Plasmodium falciparum infections (despite 7 day treatments with quinine or artesunate (+/- clindamycin) or both) with DHA-PQP. The gestational age at DHA-PQP treatment was 23.7±8.2 (9.2–39.1) weeks. 45 of the women had a known pregnancy outcome. Two infants were reported to be abnormal at birth; one with a small umbilical hernia (exposed to treatment at 24 weeks) and one diagnosed clinically with Patau syndrome (trisomy 13) (exposed to treatment at 34 weeks), who subsequently died at 6 hours of age. The remaining infants were all observed at 1 month of age and found to be healthy. The two abnormalities identified in the newborns are unlikely to be drug related. Thus, DHA-PQP was effective and well tolerated and there was no evidence of toxicity for the mothers or the newborns.

The phase four trial, or post-marketing phase, where the drugs are already in use on the markets, seeks to examine the risks and benefits of the new drug in different and larger segments of the population. This phase is important because it examines issues such as the longer-term effects of drug exposure on larger populations. Post-marketing surveillance is also important because even the most well designed phase three studies might not uncover every problem that could become apparent once a product is widely used. Furthermore, the new product might be more widely used by groups that might not have been well studied in the clinical trials and there might be reports of adverse drug reactions once a drug becomes available on the open market (African Media and Malaria Research Network, 2010).

This epidemiologic surveillance registry is necessary because of the potential for exposure in the first trimester of pregnancy and the unknown risks in pregnancy for any new chemical entity. The current lack of data regarding Eurartesim™ use during pregnancy makes such a registry an essential component of the ongoing assessment of

the safety of Eurartesim™. Through the registry, patients exposed to any formulation of Eurartesim™ during pregnancy will be registered by healthcare providers (HCPs), the pregnancies followed and the outcomes ascertained through follow-up. This information will be used to detect any potential risks to pregnant women and/or teratogenic effects in pregnancies exposed to any formulation of Eurartesim™.

This study is required in response to questions from the European Medicines Agency (EMA), to ensure that data regarding Eurartesim™ use for the treatment of malaria whilst pregnant are collected on missing populations, e.g. Caucasians.

This protocol details strategy considerations and assessment of study feasibility for a pregnancy Registry in Europe for patients exposed to Eurartesim™ whilst pregnant. The proposed pregnancy Registry is important in fulfilling the EMA post-marketing requirements.

4. Study objectives

- The primary objective of this study is to assess the live birth incidence of minor and major congenital birth defects following exposure to Eurartesim™ for the treatment of malaria whilst pregnant or in the one (1) month (30 days) prior to conception.

- The secondary objective of this study is to assess maternal, fetal and infant outcomes following exposure to Eurartesim™ for the treatment of malaria whilst pregnant or in the one (1) month (30 days) prior to conception.

5. Methodology

5.1 Study Design

A European multi-centre pregnancy Registry for patients exposed to Eurartesim™ for the treatment of malaria whilst pregnant will be compiled, incorporating Belgium, France, Germany, Italy, The Netherlands, Spain and the UK. HCPs will include all patients meeting the inclusion criteria and agreeing to take part in the Registry.

Diagnosis of malaria will be clinically and parasitologically confirmed.

TABLE 1: STUDY FLOW CHART

Assessment by HCPs	Visit 1 (Enrolment)	Visit 2 (4 weeks post-enrolment)	Visit 3 (4 weeks prior to expected due date)	Visit 4 (end of pregnancy)	Visit 5 (6 weeks after end of pregnancy)	Visit 6 (14 weeks after end of pregnancy)	Visit 7 (12 months after end of pregnancy)
Date of the visit	x	x	x	x	x	x	x
Socio-demographic characteristics	x*						
Lifestyle data	x						
Malaria history	x						
Date of exposure to Eurartesim™	x						
Pregnancy data and obstetrical history	x						
Maternal complications	x	x	x	x	x	x	
Fetal complications	x	x	x	x			
Concomitant medication use	x*	x	x	x			
Significant medical history	x*						
Exacerbation of pre-existent clinical condition		x	x	x			
Comorbidities		x	x	x			
AEs/SAEs		x	x	x	x	x	x
Maternal mortality				x	x	x	
Infant mortality				x	x	x	
Infant development					x	x	x

*These data will also be collected for the biological father.

5.2 Selection criteria

Inclusion Criteria:

The following patients will be included in the study:

- Women;
  - who have received Eurartesim™ for malaria whilst pregnant, within one (1) month (30 days) before or at any time after conception, or
  - whose partner (the biological father) has received any formulation of Eurartesim™ for malaria within one (1) month (30 days) prior to conception (Committee for Medicinal Products for Human Use, 2005), and
  - who have been informed and agree to participate in this study.

Exclusion Criteria:

The following patients must not be included in the study:

- Women who refuse to participate.
- Women participating in a clinical trial at the time of inclusion in this study.

5.3 Health Care Providers (HCP) Selection Criteria

HCPs known to treat and follow-up malaria patients will be invited to collaborate in this Registry. Women who are not part of one of the selected sites will be able to contact their HCP who will contact Sigma-Tau on their behalf in order to be included in the Registry. In addition, all patients with pregnancies reported to the company as spontaneous events by HCPs will also be asked to participate in the pregnancy Registry. All spontaneous events (e.g. pregnancy exposure, birth defects) will be reported, regardless of the country they are coming from.

An invitation letter will be sent out with a summary of the study and a reply form to identify HCPs in each country. Non-respondent HCPs will be contacted by telephone by Epidemiologic Research Associates (ERAs) trained for this study, to determine the status regarding their participating.

The reply form and qualification telephone call will enable the collection of information about the sites (e.g. speciality, type of institution/practice, number of patients seen, reasons for refusal) and the assessment of their ability and willingness to participate.

5.3.1 Educational Outreach Program

An educational 'outreach program' will be implemented to increase awareness of the Registry among both patients and Health Care Providers (HCPs), and increase both patient and HCP participation.

The awareness campaign will include the following elements in each country initiated into the study:

- Patient Information Sheet included with product packaging (including contact data for each country).
- Targeted educational material.
- Registry website and web awareness activities, including internet based recruitment.
- Advertising and scientific presentations at specifically targeted meetings such as the tropical medicine society meetings, etc.
- Partnering with interested organisations.

Educational material, targeting those in traveller's medicine and infectious disease, will inform HCPs of the Registry and provide information on how they can refer patients for inclusion and participation.

A Registry website will provide information regarding the Registry, targeted at both patients and HCPs, and will describe the process for participation for both patients and HCPs, including relevant contact details; this website will be designed with a section for patients and a section for HCPs.

Internet based recruitment, using keyword searches, will also be employed. When an internet user uses a search engine, relevant keywords (e.g. malaria, Eurartesim™) will be rerouted to the Registry website, thus, raising awareness of the Registry and providing a means of both patient and HCP participation.

Additional web awareness activities will include placing advertisements and links on relevant sites (i.e. Medicines for Malaria Venture [MMV]).

There will also be advertising at annual professional society meetings (such as the European Society of Clinical Microbiology and Infectious Diseases) to increase HCP awareness and encourage referral of appropriate patients.

In addition, the Sponsor will contact these organisations in an effort to increase awareness of the Registry to the public and HCPs:

- European Network of Teratogen Information Services (ENTIS)
- European Surveillance Network of Congenital Anomalies (EUROCAT)
- European Collaboration of Craniofacial Anomalies (EUROCRAN)
- International Clearinghouse for Birth Defects Monitoring Systems

A review of literature will be performed routinely to ensure that HCPs publishing any relevant maternal exposure are contacted for inclusion in the Registry.

5.4 Sample Size Calculation

Data for this pregnancy Registry will be regularly collected until the sample size required to detect a 2-fold or greater increase relative to the expected background rate of all birth defects and spontaneous abortions is reached. This will provide an adequate sample to ensure understanding of maternal drug safety. The Registry will be closed to new entries once this number of women with validated follow-up information has been reached and in agreement with the EMA; the data will be transferred to another independent Registry, if in acceptance with the other Registry, and according to ethical standards and national legislation at that point in time. These data will then be compared to background rates to see if there has been a significant increase in birth defects or pregnancy loss amongst these patients. A sensitivity analysis will be performed on the data to check other contributing factors.

The following sample size is derived to detect a clinically significant difference (i.e. a >2x increase in the outcome of concern) relative to expected background rates. In Europe, the assumed background risk of all reported birth defects is 23.719 per 1,000 births (EUROCAT, 2009) and the background rate of spontaneous abortion is 85.6 per 1,000 (Tata *et al*, 2005). Thus, assuming 80% power, 0.05 significance level (one-sided) and a loss to follow-up rate of 5%, we would require 376 pregnant women exposed to Eurartesim™ in order to be able to detect a 2-fold or greater increase in birth defects and a 1.5-fold or greater incidence in spontaneous abortions with a one-group test. Calculations are based on a normal approximation to a Binomial distribution (equivalent to a chi-square test). Employing a 5% loss to follow-up rate is deemed appropriate as

utilising the services of ProClinica (refer to Section 7.3) to actively follow-up patients via direct patient contact should reduce the degree of loss to follow-up in this Registry.

The method of site allocation was based on the weight according to reported malaria case-load per country (European Centre for Disease Prevention and Control, 2010) combined with the findings of the feasibility study (refer to Appendix 1). We would, therefore, require a total of 57 sites, represented across Belgium, France, Germany, Italy, The Netherlands, Spain and the UK, in order to recruit 376 patients over 5 years. For Belgium, Italy, The Netherlands and the UK, where data was currently unavailable for the feasibility study, the most conservative estimates were extrapolated from the other countries' responses. The Belgium site queried in this feasibility study did not report any recent cases of malaria among pregnant women. However, based on European Centre for Disease Prevention and Control malaria statistics (European Centre for Disease Prevention and Control, 2010), Belgium has a high reporting rate of malaria per persons among EU countries, so it has been included in the protocol to ensure adequate enrolment of pregnant women into the Registry.

Analyses and data on current recruitment rates will be provided on an annual basis. If analyses show that recruitment rates are lower than anticipated/required, attempts will be made to further increase the number of study sites, e.g. by including further countries.

5.5 Data collected

Patient's identities will remain confidential and a Patient ID number will be assigned for the purpose of communicating with the reporting HCP. Eligible patients will be asked to give signed, witnessed informed consent for the confidential release of data. The biological father will also be requested to give consent for the release of data referring to him; if the mother consents to participate in the registry but the biological father doesn't, then the mother and her infant will still be included in the registry but no data will be collected on the biological father.

In addition to data collected by HCPs during visits and in order to minimize lost-to-follow up rates, a supplementary system of active patient follow-up will be undertaken by a dedicated and independent unit, so called ProClinica (refer to Section 7.3), which is specialised in direct and proactive patient management in studies. This independence will ensure confidentiality and safekeeping of the collected data.

At study initiation, enrolling HCPs will ask patients to consent through a Contact Order Form to allow ongoing contact by ProClinica, if needed. The patients will be asked to provide their contact details, contact details of a relative and of their usual referral HCP and authorization to contact the relative then the referral HCP following an escalated contact process.

The non-reception of the iterative information from HCPs through the CRF completion in due time as scheduled in the protocol will trigger ProClinica intervention.

Triggering for this intervention will be:

- No information received from the HCP 3 months after patient enrolment
- No information received from the HCP 3 months after expected date of delivery
- No information received from the HCP 3 months after expected date of delivery + 12 months

Several attempts to contact the patient by telephone, then a relative, then the referral HCP will be performed (3 attempts for each type of contact). In case these telephone contacts are unsuccessful, a short questionnaire will be sent by mail to the patient. This process will be performed up to 3 times (according to the 3 triggering events).

The main objective of these contacts will be to remind the patient of the importance to comply with the Registry assessment schedule, to detect and document the reasons for non-collection of information (i.e. serious safety event, withdrawal from the study, personal reason).

A structured short screening of pregnancy outcome, easy to understand by patients, will be performed and documented. A copy of the completed screening questionnaire will be systematically sent to the concerned Registry HCP. Should the screening detect an abnormal pregnancy outcome and/or a serious safety event on the child, the concerned Registry HCP will be asked to follow up and medically confirm the event. If the concerned Registry HCP is not able manage this medical confirmation, ProClinica will seek to get a medical confirmation through patient treating HCPs.

All actions performed by ProClinica and information collected will be documented.

Patients will be considered lost to follow-up if a patient's expected delivery date has passed and outcome data have not been entered into the Registry within one year following the expected delivery date, and all attempts for contact failed. Reasons of loss to follow-up (e.g. patient not contactable, moved away, died) will be documented.

The following data will be collected from the HCP:

Occupation categories will be defined as recommended by EUROCAT (EUROCAT, 2009).

HCP enrolment form:

- Specialty.
- Years in practice.
- Geographic location.
- Institution type.
- Number of pregnant malaria patients currently treating.

At enrolment visit:

- Date of the visit.
- Socio-demographic characteristics of the mother (ethnicity [based on the standard definitions of ethnicity used in the EU country where the woman is enrolled in the Registry], country of birth, primary language and socio-economic status [based on current or most recent occupation and years of formal education]).
- Socio-demographic characteristics of the biological father (age and current or most recent occupation).
- Mother's lifestyle data (height [cm] and weight [kg], radiation exposure, smoking status [never/past/current], alcohol consumption [weekly units], recreational drug use.
- Mother's malaria history (date of malaria diagnosis, date of most recent Eurartesim™ administration and dose, previous Eurartesim™ administrations, other treatment taken for malaria).
- Pregnancy data (date the pregnancy was registered).
- Estimated date of delivery/date of last menstrual period.
- Previous or concurrent maternal complications.
- Health status of the fetus, if it is already known at time of enrolment, i.e. via ultrasound.
- Pregnancy outcome, if already known at time of enrolment.

- Obstetrical history (number of previous pregnancies and outcome).
- Significant medical history of the mother and the biological father.
- Concomitant medication use in the mother and the biological father in the one (1) month (30 days) prior to conception.

4-weeks post-enrolment and 4-weeks prior to expected due date:

- Date of the visit.
- Serious adverse events (drug related or not) in the mother since previous visit/contact.
- Exacerbation of pre-existent clinical condition in the mother since previous visit/contact.
- Comorbidities in the mother since previous visit/contact.
- Concomitant medication use in the mother since previous visit/contact.
- Maternal complications since previous visit/contact.
- Fetal complications since previous visit/contact; any spontaneous abortions (≤28 weeks gestation), elective abortions, ectopic pregnancies, late fetal or neonatal deaths (>20 weeks gestation), premature deliveries (≤37 completed weeks).

At end of pregnancy:

- Date of the end of pregnancy.
- Maternal complications since previous visit/contact.
- Maternal mortality.
- Stillbirth (>28 weeks gestation).
- Early neonatal mortality.
- Gestational age at delivery (estimated from the last menstrual period).
- Live births.

- Infant birth weight (adjusted for gestational age).
- Infant major and minor birth defects (primary outcome of interest).
- Serious adverse events (drug related or not) in the mother or the infant since previous visit/contact.
- Exacerbation of pre-existent clinical condition in the mother since previous visit/contact.
- Comorbidities in the mother since previous visit/contact.
- Concomitant medication use in the mother since previous visit/contact.

6 weeks after end of pregnancy:

- Date of the visit.
- Maternal complications since previous visit/contact.
- Maternal mortality.
- Early neonatal mortality (≤7 days of birth).
- Neonatal mortality (≤28 days of birth).
- Infant major and minor birth defects.
- Serious adverse events (drug related or not) in the mother or the infant since previous visit/contact.

14 weeks after end of pregnancy:

- Date of the visit.
- Maternal complications since previous visit/contact.
- Maternal mortality.
- Infant mortality.
- Serious adverse events (drug related or not) in the mother or the infant since previous visit/contact.

- Infant development.

12 months after end of pregnancy:

- Date of the visit.
- Serious adverse events (drug related or not) in the mother or the infant since previous visit/contact.

5.5.1 Infant development / assessment of pregnancy outcomes

Enrolment visit / 4-weeks post-enrolment / 4 weeks prior to the expected due date:

Pregnant women exposed to Eurartesim™ for malaria will be primarily enrolled into this Registry via their Infectious Disease Doctor. During enrolment, the patient will be asked to consent to allow ongoing contact between ProClinica (refer to Section 7.3) and her obstetrician/gynaecologist (OB/GYN), General Practitioner (GP) and Paediatrician in order to co-ordinate active follow-up and completion of the CRF at the specified time-points. Throughout the patient's pregnancy, ProClinica will support the primary investigator by contacting the patient's OB/GYN and GP in order to obtain medical confirmation of events occurring, e.g. SAEs, comorbidities, maternal complications, fetal complications.

At birth:

At birth, ProClinica will contact the patient's OB/GYN and GP to obtain medical confirmation of events occurring, e.g. premature delivery, still birth, birth defects.

6 weeks after end of pregnancy / 14 weeks after end of pregnancy / 12 months after end of pregnancy:

After birth, ProClinica will contact the infant's Paediatrician to obtain medical confirmation of events occurring, e.g. birth defects, infant development, neonatal death.

"Birth defect" will be defined as a major congenital abnormality or syndrome with exclusion for related minor abnormalities, as defined by EUROCAT (EUROCAT, 2009). HCPs will record any infant birth defect(s) on the CRF via free text. This will then be coded in-house using both MedDRA and ICD-10 codes (ICD-10 Chapter XVII: congenital malformations, deformations and chromosomal abnormalities, as recommended by EUROCAT) to enable comparisons and transfer of data between other sources.

5.6 Monitoring visit

CRAs (Clinical Research Associates) will perform on-site monitoring visits for data quality checking in 20% of total sites dependent on an escalated monitoring procedure, which considers the compliance of each site with study procedures. The aim of these on-site visits will be to check the correct collection of informed consent, check key data of the CRF against the source data on a defined percentage of patients, check the correct reporting of adverse reactions according to the protocol and communicate with the HCP. These monitoring visits will also enable the CRA to resolve any administrative issues, potential logistical problems raised by the HCP and to discuss the recruitment of patients and compliance.

5.7 Statistical analysis

Statistical analyses will be carried out using SAS software version 9.2.

R-M EU will prepare a statistical analysis plan to be reviewed by Sigma-Tau and the CAB.

At regular intervals tables and listings will be produced to enable reporting of key interim outcomes to regulatory authorities, participating HCPs and the scientific/medical community at large.

Reporting of data (other than individual reports concerning individual patients or participating HCPs to those individual participants), will be in aggregate form to ensure individual patient and HCP confidentiality.

All analyses, primary and secondary, will be conducted in two manners:

1. On all women.
2. Stratifying the women depending on whether they were directly exposed to Eurartesim™ or whether the biological father was exposed to Eurartesim™.

Primary analysis

In accordance with the primary objectives of the study and the way the study was powered, the main focus of the statistical analysis will be estimation of the incidences of birth defects and spontaneous abortion. 95% confidence intervals will be computed around these incidences in order to judge whether there is an increase of these incidences as compared to background risks.

In order to control for potential confounders, birth defects and spontaneous abortion will be described according to parameters such as concomitant infections/diseases and medication use.

For spontaneous abortions, women who discontinued the study prior to delivery will not be taken into account in the primary analysis. A sensitivity analysis will be performed considering all patients, assuming that women who discontinued the study prior to delivery had experienced spontaneous abortion; this will provide us with the highest estimation of incidence of spontaneous abortion (i.e. the worst-case scenario).

In the same way, in the primary analysis, incidences of birth defects will be analysed without considering patients who discontinued the study prior to 14 weeks after the end of pregnancy. A sensitivity analysis will be performed on all patients assuming that women who discontinued the study prior to 14 weeks after the end of pregnancy had experienced birth defects.

Description of the study populations

- HCPs:

HCPs will be described according to the data included in the HCP enrolment form. Tables and listings describing participating HCP characteristics will be produced (specialty, years in practice, geographic location, institution type, number of pregnant malaria (Registry) patients treated/site).

- Patients:

Patients included in the study will be described according to demographic and background characteristics (e.g. age, ethnicity, duration and timing of exposure to Eurartesim™).

Pregnancy-related information

Frequency and type of pregnancy outcome will be stratified by the earliest trimester of exposure, demographics and medical background characteristics. Gestational weeks will be counted from the date of the last menstrual period, with the second trimester as beginning at week 14 and the third trimester as beginning at week 28. Women who discontinued the study prior to delivery will not be taken into account in the primary analysis. A sensitivity analysis of patients who did not complete the entire follow-up will be performed for the main study outcomes, in the same manner as described above in the 'Primary analysis' section.

Time-to-event variables will be analysed via survival analysis methods (e.g. Kaplan-Meier survival estimates and associated confidence intervals).

In order to control for potential confounders, pregnancy outcomes will be analysed according to parameters such as lifestyle factors, concomitant infections/diseases and medication use. Patient's Body Mass Index (BMI) will be calculated from the patient's height (cm) and weight (kg) data, using the following equation:

$$BMI = \frac{\text{Weight (kg)}}{\text{Height (meters)}^2}$$

The BMI outcome value will be categorised as follows:

- BMI <18.5 = Underweight
- BMI 18.5-25 = Healthy weight
- BMI >25 = Overweight

In order to optimize patient recruitment, patients with recurring malaria and Eurartesim™ use during pregnancy will be included in this pregnancy Registry in addition to first malaria infections. However, first and recurring malaria infections will be analyzed separately due to the potential differences in disease aetiology and pregnancy outcomes.

Analytical methods

Continuous variables will be described by their mean, standard deviation, median, quartiles 1 and 3, extreme values (minimum and maximum) and the number of missing data.

Categorical variables will be described by the total and percentage of each response method and the number of missing data.

Continuous variables will be compared using Student's t-test (2 groups) or variance analysis (>2 groups). If the conditions for applying these tests are not met (normality, homoscedasticity), the Mann-Whitney, Wilcoxon (2 groups) or Kruskal-Wallis (>2 groups) non-parametric tests will be used.

Categorical variables will be compared between subgroups using the Chi-2 test if the theoretical total of each class studied is greater than 5. Otherwise Fisher's exact test will be used.

The ordinal variables will be compared between subgroups using a Cochran-Mantel-Haenszel test.

Hypothesis formulation will be bilateral. The tests will be performed for a first species alpha risk of 5%.

6. Bias and limits of the study

Generally, three types of bias are distinguished in epidemiology and should be considered: selection, information and confounding bias. Potential biases and limitations of the Eurartesim™ pregnancy Registry include:

6.1 Selection bias

Selection bias is a distortion of evidence or data that arises from the way that the data are collected.

The selection bias that could possibly occur in this study are related to the selection of the participating HCPs and the selection of patients.

HCP's representativeness:

The participating HCPs will consist of a population of volunteers; this constitutes a classical non-response selection bias for this type of study.

To describe this potential bias, we propose to compile a HCP recruitment registry in order to collect information (e.g. age, gender, speciality, geographic region, mode of practice, institution type) for all the contacted HCPs and for all the HCPs that initiate a contact themselves, participating or non-participating to the study. The reasons for non-participation will also be collected in the registry. These data will allow comparison of the characteristics of participating and non-participating HCPs.

Patient's representativeness:

In order to limit the patients' selection bias, the HCPs will have to consecutively include all the patients meeting the selection criteria. For all non-included patients meeting the selection criteria, the HCP will collect few data (e.g. age, gender, reason for non-inclusion), in order to allow comparison of the characteristics of included and non-included patients.

It is anticipated that the primary limitation encountered when compiling this pregnancy registry will be patient recruitment as there may be very few women across Europe who have had malaria and also taken Eurartesim™ to treat such whilst pregnant. Thus, recruitment will be kept simple to optimize patient recruitment, i.e. both first and recurrent malaria infections will be included in this pregnancy Registry. This approach will be evaluated throughout the feasibility study and via discussions with Key Opinion Leaders in this field. Patient recruitment and data collection will be conducted as described above in this protocol.

Selection bias could also occur in this study regarding the inclusion of women who already know the health status of the foetus at the time of enrolment into the pregnancy registry, as patients with a known undesirable outcome may be more likely to enroll than

those with a known healthy outcome. However, due to the possible limitations regarding patient recruitment (as discussed above), women who already know the health status of the foetus at the time of enrolment into the pregnancy registry will still be eligible for inclusion.

6.2 Information bias

Information bias is a distortion in the estimate of association between risk-factor and disease that is due to systematic measurement error or misclassification of patients on one or more variables, either risk-factor or disease status. This could occur in this study if HCPs do not report certain types of events of potential interest because they feel they are not related to the safety of the medication. As a result, we will check key data of the CRF against the source data for a defined percentage of patients to determine how well the information provided in the Eurartesim™ Registry matches their medical records.

Misclassification of timing of exposure; it may be difficult to ascertain at exactly which point throughout the pregnancy the exposure to Eurartesim™ occurred.

Outcome misclassification; there is a likelihood that pregnancy losses occurring early in gestation (i.e. the first trimester) may not be recognized and/or reported. Additionally, the reporting HCP may not always know the health status of aborted fetuses.

Ascertainment of elective abortions; legislation in some countries may prohibit the collection of identifiable data. Elective abortion is currently legally available in all European countries, except Malta. All of these countries allow abortion to save the life of a mother and most for other reasons, including on-demand up to 18 weeks of gestation (BBC News, 2007). As a result, it seems unlikely that assessment of elective abortion (without additional information for the reasons associated with abortion) would violate local laws in the countries being targeted for patient enrolment. In addition, however, prior to initiation of recruitment in a given country, the Sponsor and it's designated CRO partner, REGISTRAT-MAPI, will review local laws for each country and discuss the specific questions to be used on this topic with the local investigators and relevant ethical committees and authorities to ensure that the necessary wordings are considered with regards to current interpretation of ethical standards and applicable local laws.

Information bias could also occur in this registry regarding the collection of lifestyle data, such as BMI, radiation exposure, smoking status, alcohol consumption and recreational drug use. Patients may under-report these factors, which is an inherent limitation associated with the collection of lifestyle data.

6.3 Confounding bias

Concomitant infections/diseases and medication use may have a potential confounding influence upon the pregnancy outcome and maternal complications. In order to control for potential confounders, details of any concomitant infections/diseases and medication use will be collected and pregnancy outcomes will be analysed according to these parameters.

6.4 Lost to follow-up

Outcomes among pregnancies lost to follow-up could differ from those with reported outcomes. Patients will be considered lost to follow-up if a patient's expected delivery date has passed and outcome data have not been entered into the Registry within one year following the expected delivery date. Reasons of loss to follow-up will be documented. In order to investigate this further and determine the extent to which the results may be affected by loss to follow-up, a sensitivity analysis will be executed, in the same manner as described in the 'Primary analysis' part of Section 5.7.

In order to reduce the number of lost to follow-up patients, the option for each patient to be contacted by a specialized patient management unit (ProClinica, refer to Section 7.3) run by our CRO partner has been built into the Registry. Such contact will provide ongoing patient contact to remind the patient-participant of the importance of her ongoing participation in the Registry.

7. Study Conduct

7.1 Site initiation

A study kit will be given to each HCP who confirms his/her participation and completes the necessary administrative procedures.

The study kit contains the following:

- Protocol
- Patient information sheet and consent form
- (Serious) Adverse Event Report
- Contact Order Form (COF)
- HCP enrolment form
- Pre-paid envelopes

On reception of the study kit, a HCP initiation phone call will be performed by the responsible ERA to review the study and its logistic and administrative aspects.

As they are completed, the HCP enrolment forms will be returned to RM-EU by the HCPs in prepaid envelopes just after the visit.

7.2 Patients' inclusion

The HCP will include all patients meeting the inclusion criteria and agreeing to take part in the Registry. During this recruitment phase, and for each patient, the HCP will:

- Explain the Registry to the patient (in particular the objective of the registry and its observational nature), give her a patient information sheet, a Consent Form and a Contact Order Form and ask the patient to read, fill in and sign them to confirm her agreement.
- Fill in the enrolment CRF of the registry.
- Send by fax or mail the completed Contact Order Form to the unit in charge of the patient follow-up.

These agreements must be obtained for the recruitment and follow-up of both the patient and her infant.

For non-included patients meeting the selection criteria, the HCP will collect few data (e.g. age, ethnicity, gestational time of Eurartesim™ exposure) in a short form (patient

log) of the Registry to collect the reason of non-inclusion and in order to determine if the study population correspond with the wider population.

7.3 Follow-up

During follow-up visits/contacts, the HCP will:

- Fill in the follow-up CRF of the registry.

Women will visit their antenatal clinic for assessment of safety parameters at enrolment, 4 weeks post-enrolment, 4 weeks pre-delivery, at delivery and at 6 weeks post-delivery. Infants will be followed up at 6 weeks, 14 weeks and 12 months after birth. Infant neuro-developmental assessment will be performed at 14 weeks and 12 months after birth. Safety assessments will include monitoring and recording all AEs and SAEs up to 12 months after delivery; in the case of the reporting of an adverse outcome, additional information regarding relevant medical history and family history will be collected.

Ethical and Personal Data Protection considerations regarding contacts with Patient:

Patients or their legal representative are asked to complete and sign a "Contact Order Form". This "Contact Order Form" is sent to ProClinica. From an ethical and personal data protection perspective, this written patient agreement provides evidence that the participant and/or his legal representative voluntarily communicated his personal and his HCP's contact details to the ProClinica unit. This will allow them to perform the contacts as described in the protocol during the study follow-up period.

Additionally, by this form patients are informed about their rights, as required by the Data protection regulations. Given that the patient has the right to refuse to answer the questionnaire or individual questions at any time and may ask the ProClinica unit to end all future contacts, it can be considered that consent to be contacted and to provide health information is tacitly renewed with each assessment.

The ProClinica unit never transfers patients' nominative data to the study sponsor, the monitor or any other third party not directly involved in its mission. Patients' health data are collected in a de-identified way, using a study identification code (e.g. patient number, site number). The patients' contact details are never linked to the patients' health data and the patients' contact details, including Contact Order Forms, are erased at the end of the study from all data support systems (computer and paper).

All interviewers working on the study have signed a professional secrecy agreement, are trained specifically to the study and to data privacy rules, as well as supervised and quality controlled throughout the study. The Medical Direction of ProClinica unit will intervene when necessary. Patient return calls by a HCP can be performed when needed.

The ProClinica unit personal should not be considered as a substitute for the investigator or the treating HCP in their patient follow-up responsibilities. Interviewers never interfere with the usual relationship between patients and healthcare professionals. On the contrary, they promote it. They are required to not comment any prescription or giving any advice or response to medical/study questions (except for those expressly included in their mission for the project). If a medical question or problem arises during a telephone call, the patient (or the legal representatives) is advised to contact his/her HCP.

REGISTRAT-MAPI has declared its ProClinica unit activities of direct contact with patients in studies and patient management programs to the French Data Protection Authority (CNIL) (refer to Appendix 2). This declaration (statement number 794019) covers the management of patient contact details throughout the European Union (i.e. administrative data). Collection of health data should be submitted to competent authorities according to each country specific regulations.

The processing of personal data is performed in accordance with REGISTRAT-MAPI commitment (statement number 1432965) to comply with the French standards for Pharmacovigilance activities *(Autorisation unique AU-013 pour le traitement des données à caractère personnel dans le cadre de la pharmacovigilance)*.

7.4 Data collection

R-M EU will develop a formalized CRF for data collection purposes.

Patients' identities will remain confidential and a Patient ID number will be assigned for the purpose of communicating with the reporting HCP.

"Birth defect" will be defined as a major congenital abnormality or syndrome with exclusion for related minor abnormalities, as defined by EUROCAT (EUROCAT, 2009). HCPs will record any infant birth defect(s) on the CRF via free text. This will then be coded in-house using both MedDRA and ICD-10 codes (ICD-10 Chapter XVII: congenital

malformations, deformations and chromosomal abnormalities, as recommended by EUROCAT) to enable comparisons and transfer of data between other sources.

7.4.1 Outcomes of potential interest

Data for the following outcomes will be collected:

Primary outcome:

- Live birth incidence of minor and major congenital birth defects following exposure to Eurartesim™ for the treatment of malaria whilst pregnant.

Secondary outcomes:

- Maternal complications.
- Maternal mortality (up to 6 weeks post-delivery).
- Spontaneous abortions (≤28 weeks gestation).
- Elective abortions.
- Ectopic pregnancies.
- Stillbirth (>28 weeks gestation).
- Premature deliveries (≤37 completed weeks).
- Early neonatal mortality (≤7 days of birth).
- Neonatal mortality (≤28 days of birth).
- Gestational age at delivery (estimated from the last menstrual period).
- Low birth weight (adjusted for gestational age).
- Infant development.

7.5 Data management processes

A database will be programmed in ORACLE™ to receive the information collected in the registry. This will include automated edit checks. Data entry screens and edit checks will be validated with test data prior to commencing the formal database entry. Concomitant medications will be coded according to the current version of the WHODrug. Medical history and diseases will be coded according to the current version of the Medical Dictionary for Regulatory Activities (MedDRA). A data handling manual including edit check specifications, data entry guide, tracking guide, authorized corrections, coding instructions, and locking procedure will be written as an operational benchmark.

HCPs will be asked to complete the registry at the different time points.

When discrepancies are identified in the registry, the data management group will issue data correction requests. Resolutions to these queries will require re-authorisation of the HCP.

A final validation of the database will be performed and the database locked before statistical analysis is conducted.

7.6 Adverse events

7.6.1 Definitions

An adverse event (AE) is defined as any untoward medical occurrence in a patient, which does not necessarily have a causal relationship with their treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the labelling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event.

If an adverse event meets any of the following criteria, it is considered a **serious adverse event (SAE):**

- **Death of Patient:** An event that results in the death of a patient.
- **Infant Mortality:** Death of child following live birth
- **Life Threatening:** An event that, in the opinion of the HCP, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.

- **Hospitalization:** An event that results in an admission to the hospital for any length of time. This does not include an emergency room visit or admission to an outpatient facility.
- **Prolongation of Hospitalization:** An event that occurs while the study patient is hospitalized and prolongs the patient's hospital stay.
- **Congenital Anomaly:** An anomaly detected at or after birth, or any anomaly that results in fetal loss.
- **Persistent or Significant Disability/Incapacity:** An event that results in a condition that substantially interferes with the activities of daily living of a study patient. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
- **Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome:** An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the patient and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e*.,* death of patient, life-threatening, hospitalisation, prolongation of hospitalisation, congenital anomaly, or persistent or significant disability/incapacity). Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse, misuse, diversion, accidental exposure, and use in opioid naive patients.
- **Spontaneous Abortion:** Miscarriage experienced by study patient.
- **Elective Abortion:** Elective abortion performed on study patient.

The HCP will use the following definitions to rate the severity for any adverse event being collected as an endpoint/datapoint in the study and for all serious adverse events.

- **Mild:** The adverse event is transient and easily tolerated by the patient.
- **Moderate:** The adverse event causes the patient discomfort and interrupts the patient's usual activities.
- **Severe:** The adverse event causes considerable interference with the patient's usual activities and may be incapacitating or life-threatening.

The HCP will use the following definitions for any adverse event being collected as an endpoint/datapoint in the study and for all serious adverse events, to describe the relationship of the adverse event to the use of Eurartesim™:

- **Unsuspected – not related to use of medication;**
- **Suspected – potentially related to use of medication.**

7.6.2 Serious Adverse Event Reporting

By Registry HCP

In the event of a serious adverse event (as defined in Section 7.6.1), in addition to the data collected on the CRF, the HCP will notify both REGISTRAT-MAPI and Corporate Drug Safety of Sigma-Tau **within 24 hours** of the HCP becoming aware of the event, using the SAE Form provided.

The completed and signed SAE form shall be sent to:

REGISTRAT-MAPI Drug Safety Department

e-mail: safety.eu@registratmapi.com

Fax number: +33 (0)4 72 13 39 99

Safety phone number: +33 (0)4 72 13 55 88

and to:

Sigma-Tau Corporate Drug Safety

e-mail: pharmacovigilance@sigma-tau.it

Fax number: +39 (0)6 9139 4007

Safety phone number: +39 (0)6 9139 3339

REGISTRAT-MAPI will be responsible for contacting the reporting HCP to obtain any missing information on the SAE form. REGISTRAT-MAPI will provide this information to Sigma-Tau to allow it to conform with all international expedited reporting requirements.

By ProClinica and REGISTRAT-MAPI:

In addition to solicited reporting of adverse events, as described in this protocol, spontaneous reporting of a potential adverse drug reaction to a Sigma-Tau product may occur during a contact. These cases are managed in accordance to a standardized reporting procedure and/or according to the project specific Safety Management Plan.

REGISTRAT-MAPI personnel and Contact platforms involved in the project will be trained about their obligation of reporting in that matter.

Following a case notification from the contact platform or REGISTRAT-MAPI personnel, REGISTRAT-MAPI Drug Safety Unit will be in charge of reporting to Sigma-Tau Pharmacovigilance according to the study specific Safety Management Plan.

By Sigma-Tau:

Sigma-Tau pharmacovigilance will be in charge to report individual cases (spontaneous and solicited safety cases) to the concerned health authorities.

Case processing and expedited and/or periodic reporting modalities will be defined in a Safety Management Plan in accordance with Volume 9A, and particularly, for pregnancy cases, with chapter I.5.4 "Reporting of Outcomes of use of a Medicinal Product During Pregnancy" and related guidances, including, but not limited to, "Guideline on the exposure to medicinal products during pregnancy: need for post-authorisation data".

8. Registry timelines

These timelines are based on Eurartesim™ being available on the market by June 2012:

Validation of study documents:	June 2012
Ethics submission:	June 2012
Launch of Eurartesim™:	June 2012
First patient in:	July 2012
Recruitment rate analyses:	December 2012, and every 1 year thereafter
Interim statistical analyses:	June 2014, and every 2 years thereafter
Last patient in:	May 2017
Final Clinical Study Report:	September 2019

9. Ethics considerations

9.1 Ethical Conduct of the Study

The study should be conducted in compliance with the protocol, Good Epidemiology Practice guidelines, the ethical principles arising from the Declaration of Helsinki revised in 1989, and all current local regulations.

Participating HCPs are assured by the initiator of the study that it will be conducted in accordance with the provisions of the above regulations and principles and that it will meet current laws and practices.

The data collected during the study will be obtained from medical notes and information provided by the patients.

The study will not alter the treatment management of the patients and no invasive procedures or special surveillance measures are required by the protocol.

9.2 Submissions

9.2.1 Ethics Committee (EC)

Ethical submissions will be performed as required by local legislation in each country involved in the study. The necessary ethical approvals will be obtained for each site before initiation of the site. The study is observational. Choice by the HCP of the drug used to treat the patient is based on clinical judgement alone, and as such does not come under the European Directive on clinical trials, as no drug is provided by the sponsor or any third party. No specific examinations or lab tests are to be performed above and beyond those usually undertaken by the HCP, and no additional visits are required for study purposes.

9.2.2 Competent Authorities

Submissions and/or notification to competent authorities will be performed as required by local legislation in each country for this type of study.

9.2.3 Data Protection

The patient's personal data and Investigator's personal data which may be included in the Sponsor database shall be treated in compliance with all local applicable laws and regulations.

Data protection submissions to competent authorities will be performed as required by local legislation in each country involved in the study.

When archiving or processing personal data pertaining to the Investigator and/or to the patients, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

The use of indirectly named data is essential for the following reasons:

- It is essential to combine the data from the CRFs for the statistical analysis. These documents will therefore be identified by two numbers: HCP number and patient number.

- Quality control of the data will be done with the HCPs in order to guarantee the data quality, with possible correction requests for missing or inconsistent data on key data.

The patient will be informed of his/her right of access, objection and correction of the data recorded during this study, and that this right may be exercised at any time through his/her HCP.

Information relating to participating HCPs will be declared and the HCPs will be informed – within the framework of their financial agreement – of their right to access, object to and correct this information.

The process used by ProClinica (refer to Section 7.3) has been validated and approved in line with European regulations, and has been declared to the French data protection authority (i.e. the CNIL; acknowledgment of receipt n° 794019), including safety data protection measures in place for the retention of personal information and the management of direct patient contacts (refer to Appendix 2). According to European Directive, this declaration to the CNIL for processing contact details is valid across the European Union member states for all studies undertaken by ProClinica.

The collection of health data during contacts and its transfer to authorized third parties after encoding (indirectly named data) for the purpose of this Registry will be submitted to competent authorities as required by local regulations in each country involved in the study.

9.2.4 Information and patient consent

The HCP will give the patient a patient information form at the inclusion visit. This form will contain information concerning the nature and purpose of the study, the collected data, the physical persons or legal entities who will be the recipients of these data, and the patients' right of access, correction or objection to the processing of these data (in accordance with the European Directive 95/46/EC on the protection of individuals with regard to the processing of personal data and free movement of such data and its transposition in the amended "Data processing and privacy" French law of 6 January 1978).

Before any procedure associated with the study is carried out, the patient information form should be signed and dated by the patient, and by the HCP, in two copies. One copy will be kept by the patient (duplicate) and the other (the original) will be kept by the HCP in the patient's medical file.

Additionally, the patient will complete and sign a Contact Order Form allowing ProClinica to manage the follow-up contacts. One copy will be kept by the patient (duplicate), one copy will be kept by the HCP in the patient's medical file (duplicate) and the other (the original) will be sent to ProClinica.

These agreements must be obtained for the recruitment and follow-up of both the patient and her infant.

10. Final report and publications

At the end of the study, R-M EU will provide a final study report that will be reviewed by Sigma-Tau and the Clinical Advisory Board. This report will contain a description of the objectives of the study, the methodology, the results and the conclusions of the study. The completed CRFs and the study report must be treated as the confidential property of Sigma-Tau and may not be released to unauthorized people in any form (publications or presentations) without express written approval from Sigma-Tau. Interim reports will be produced, including all reports from the Registry and actual recruitment rates, and the same procedures and rules will apply.

11. Retention of study documentation

R-M EU will maintain the data collected (questionnaires and databases) for 2 years (or a longer retention period if specified and authorised) after the study has been completed.

12. Coordination

Sigma-Tau initiated this project, under the supervision of:

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REGISTRAT-MAPI, a CRO specialising in the conduct of international post-authorisation safety studies and pregnancy registries has been charged by Sigma-Tau with ensuring the collection and monitoring of the data, under the responsibility of:

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Appendix 1: Feasibility Study

A feasibility study was conducted in November/December 2010 to assist with the development of this protocol. A number of KOLs from Belgium, France, Germany, Spain and the UK were contacted and asked questions regarding the feasibility of compiling such a Eurartesim™ pregnancy Registry. A summary of this feasibility study is detailed in Table 2 below.

From the feasibility study, it is anticipated that the primary limitation encountered when compiling this pregnancy Registry will be patient recruitment, as there may be very few pregnant women across Europe who also have malaria. Additionally, it is anticipated that very few of these patients will be Caucasian; which was a request of the EMA, to ensure that data regarding Eurartesim™ use for the treatment of malaria whilst pregnant are collected on missing populations, e.g. Caucasians.

Due to the limitations surrounding patient recruitment rates, it would not be advisable to restrict the inclusion criteria of this study solely to Caucasian women across Europe exposed to Eurartesim™ for the treatment of malaria whilst pregnant. However, we anticipate that a number of Caucasian women will be enrolled in this Registry, due to the demographics of the seven European countries participating in this study.

TABLE 2: SUMMARY OF FEASIBILITY STUDY FINDINGS

	BELGIUM (n=1)	**FRANCE (n=5)**	**GERMANY (n=1)**	**SPAIN (n=2)**	**UK (n=1)**
1. Ability to identify pregnant women with malaria?	NO	YES	YES	YES	No response
If YES, how many pregnant women with malaria have you encountered over the last 12 months?	/	37	2	<5 women	/
Of these pregnant women with malaria, how many were treated with an antimalarial?	/	37	2	All of them	/
How many of these women were Caucasian?	/	Mostly African patients, very few Caucasian patients	1	0	/

	BELGIUM (n=1)	**FRANCE (n=5)**	**GERMANY (n=1)**	**SPAIN (n=2)**	**UK (n=1)**
2. How long do you think you would you need to recruit 20 women treated with Eurartesim™ for malaria whilst pregnant?	/	5 years	5 to 20 years	Not thought to be possible	/
3. Do you have the ability to obtain information on treatment, co-morbidities and other patient characteristics from your medical records?	/	YES	YES	YES	/
4. Do you have the ability to follow-up patients in order to determine the pregnancy outcome (both maternal and fetal)?	/	YES	YES	YES if the follow-up is not too long	/
5. Do you have the ability to follow-up the infants for a period of 12 months after birth to assess their neuro-development?	/	YES	YES	YES	/
6. Is it possible for patients that you identify to be enrolled into a registry?	/	YES	YES	MAYBE	/
7. Would it be possible to have your data included in a combined database held by REGISTRAT-MAPI or would you need to hold your information?	NO	YES	Depends on type of database and what information will be included.	MAYBE	/
8. Are you able to accept pharmaceutical company funding?	YES	YES	YES	YES	/

	BELGIUM (n=1)	**FRANCE (n=5)**	**GERMANY (n=1)**	**SPAIN (n=2)**	**UK (n=1)**
9. What other considerations would you have in participating in this type of study?	Very difficult to recruit Caucasians patients, not sure they will use Eurartesim™	Depends if it will be conducted in African or Caucasian patients. If it is in Caucasian patients, this may take 100 years!	Pregnant women with malaria are quite rare. May treat 2 or 3 patients per year.	If the study is limited to Caucasian pregnant patients it will last many years (3 to 5 years in order to recruit 50 patients).	/

Appendix 2: ProClinica CNIL Authorisation

CNIL
Commission Nationale de l'Informatique et des Libertés
(French Data Protection Authority)

Sylvie ODEZENNE Traducteur Expert près la cour d'Appel de Grenoble ALLEMAND ANGLAIS

Acknowledgement of receipt of ordinary declaration

Mr Xavier FOURNIE
MAPI SAS REGISTRAT-MAPI
DIVISION PROCLINICA - DIRECTION MEDICALE
27 RUE DE LA VILLETTE
69003 LYON - FRANCE

In accordance with the Act of 6 January 1978 relative to computers, files and liberties, modified in August 2004,

MAPI SAS REGISTRAT-MAPI
27 RUE DE LA VILLETTE 69003 LYON - FRANCE
Phone: +33 (0)472136680 Fax: +33 (0)172135962

Declared to the *Commission Nationale de l'Informatique et des Libertés* (CNIL) a processing of personal data whose main purpose is to:

MANAGE CONTACTS WITH PATIENTS TAKING PART IN STUDIES AND LOGISTIC ASSISTANCE ACTIONS

Reason for the modification:
- PROCLINICA became a division of the MAPI Company, but it keeps its functional autonomy
- The period of retention of data pertaining to reimbursement of expenses has been set to 10 years.

The issuance of this acknowledgment of receipt certifies that you declared your data processing to the CNIL and that your file is formally complete. You are authorised to implement your data processing. However, the CNIL may at any time verify, by mail or by means of an inspection on site, that said data processing complies with all the provisions of the Act of 6 January 1978 modified in 2004. In any case, you must comply with the obligations provided by the Act, in particular as regards:

1) The definition and compliance with the purpose of the data processing,
2) The relevance of the processed data,
3) The retention of said data for a limited period,
4) The safety and confidentiality of said data,
5) Compliance with the rights of the persons concerned: information on their rights of access and their rights to correction and object.

For further details on the obligations provided for by the "Loi informatique et libertés" (Data Protection Act), please visit the CNIL website: "www.cnil.fr".

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Paris (France), 15 March 2011

Alex Türk

By delegation of the Authority

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