SAFETY REGISTRY FOR EURARTESIM™

Pharmaco-epidemiological study protocol

Protocol N° 3381

Sponsor:	Sigma-Tau
Version:	6.0
Amendment:	
Date :	11 June 2012

CLINICAL ADVISORY BOARD

The role of the clinical advisory board (CAB) is:

- to validate the objectives and methodology of the registry
- to validate the results
- to monitor safety and enrolment rate

This CAB will be constituted of selected local country Key Opinion Leaders (cardiologists and malariologists) plus an expert in pharmacovigilance and a statistician, and will act as a scientific advisory board to review and provide guidance on the registry procedures. This CAB will meet at regular, pre-defined time-points. The main responsibility will be monitoring of safety and enrolment rate. If the latter is far from expectations, a corrective action plan will be finalised, in agreement with the Sponsor and EMA. A Charter will be in place to define the roles, responsibilities and procedures in more details.

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LIST OF ABBREVIATIONS

ACT	Artemisinin-based Combination Therapy
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
bpm	Beats Per Minute
CAB	Clinical Advisory Board
CCTIRS	Advisory Committee on Information Processing in Material Research in the Field of Health
CNIL	French National Commission for Data Processing and Privacy
CNS	Central Nervous System
COF	Contact Order Form
CRA	Clinical Research Associate
CRO	Clinical Research Organisation
CRF	Case Report Form
DHA	Dihydroartemisinin
EC	Ethics Committee
ECG	Electrocardiogram
EMA	European Medicines Agency
ERA	Epidemiologic Research Associate
HCP	Health Care Provider
ICF	Informed Consent Form
KOL	Key Opinion Leader

MedDRA	Medical Dictionary for Regulatory Activities
MMV	Medicines for Malaria Venture
PASS	Post-Authorisation Safety Study
PQP	Piperaquine
QTc	Corrected QT segment length
QTcB	Corrected QT segment length – Bazett correction
QTcF	Corrected QT segment length – Fridericia correction
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
TdP	Torsade de Pointes

1. SUMMARY

Title of the study	Safety Registry for Eurartesim™.
Registry design	A multi-centre safety registry for malaria patients treated with Eurartesim™.
Registry objectives	**Primary objective:** - To study the association between safety parameters (in particular QTc prolongation) and the following factors: • Age. • Gender. • Ethnicity. • Lifestyle (smoking status, alcohol consumption). • Food intake (time). • Co-morbidities. • Co-medications. **Secondary objectives:** - To estimate the incidence of QTc prolongation following Eurartesim™ initiation. - To estimate the incidence of all and each individual pre-specified treatment-emergent adverse events of special interest (AESI) following Eurartesim™ initiation. The following events are defined as AESIs: • Torsade de Pointes (TdP). • Sudden death. • Ventricular tachycardia. • Ventricular fibrillation and flutter. • Syncope. • Seizures. • Sustained arrhythmias (repetitive or lasting >30 sec at a ventricular rate >120 bpm). - To estimate the incidence of all adverse events (AEs) and serious adverse events (SAEs) following Eurartesim™ initiation, including neurotoxicity and phototoxicity. - To assess the relationship between QTc prolongation and the AESIs, AEs and SAEs.
Methodology	This is an observational, non-comparative, non-interventional longitudinal study. As an observational study, this registry will not change the patient-HCP relationship, nor influence the HCP's drug prescription or therapeutic management of the patient. Thus, as per the Eurartesim™ Summary of Product Characteristics (SmPC), only when deemed clinically appropriate by the patient's HCP, an ECG recording will be conducted as soon as possible after patient enrolment into the registry (preferably before the first Eurartesim™ dose) and then before and after the last Eurartesim™ dose. HCPs will each be asked to include all patients meeting the eligibility criteria and agreeing to take part in the registry. Paediatric patients (<18 years of age) may also be enrolled for inclusion in the registry. If a paediatric patient is enrolled, the child's parent must provide informed consent for their child's data to be collected and provide follow-up contact information to ProClinica™. The registry will be closed to new entries once 300 patients with validated data have been enrolled. This closure will be in agreement with the EMA. During the recruitment phase, and for each patient, the HCP will:

	- Explain the registry to the patient (in particular the objectives of the registry). - Give him/her a patient information sheet and consent form and ask the patient to read and sign it to confirm his/her agreement to participate in the registry. - Complete the enrolment CRF (to be posted to REGISTRAT-MAPI). - Explain the role of ProClinica™ to the patient and ask the patient to complete and sign a Contact Order Form (COF) (to be faxed to ProClinica™). - Give the patient a concomitant medication use diary and ask the patient to complete this (i.e. medication names and prescription dates) for the duration of the registry follow-up. Before any procedure associated with the registry is carried out, the patient information and Informed Consent Form (ICF) should be signed and dated by the patient. Data will be collected during the normal course of patient care. According to routine clinical practice, most patients receiving Eurartesim™ for the treatment of malaria will be hospitalised for at least three days and follow-up (including the recording of ECG and blood withdrawing results) will be conducted at hospital discharge. For the minority of patients who refuse hospitalisation, follow-up (including the recording of ECG and blood withdrawing results) will be performed on an out-patient basis and the patients will be asked to contact their HCP with these test results, in order for the data to be recorded on the CRF. A follow-up visit is also recommended between three to five weeks after hospital (or out-patient treatment) discharge. During the follow-up visits, the HCP will: - Complete a follow-up CRF. - Post the follow-up CRF to REGISTRAT-MAPI in the pre-paid envelope, following the visit. Patients will remain in the registry even if a visit is not performed. It is anticipated that some patients may not attend the follow-up visit at three to five weeks after hospital (or out-patient treatment) discharge. ProClinica™ will contact the participating patients for follow-up by telephone after 15 days following Eurartesim™ initiation should the follow-up visit at hospital (or out-patient treatment) discharge not be completed, and 45 days following Eurartesim™ initiation should the follow-up visit at three to five weeks after hospital (or out-patient treatment) discharge not be completed. Patients will be flagged for telephone follow-up by ProClinica™ if their corresponding CRF has not been received after 15 days and 45 days, respectively. During these follow-up telephone calls, ProClinia™ will collect data regarding: - Concomitant medication use since last follow-up, including any other treatment taken for malaria (including prescription dates). - Any AEs/SAEs/AESIs since last follow-up. - Patient status. In order to aid patient recall of concomitant medication use since the last follow-up (i.e. medication names and prescription dates) and enhance the reliability of the concomitant medication use data collection during these follow-up telephone calls, a patient diary will be employed. At the registry enrolment visit, all patients will receive a diary and be asked to record the names of any medications used and the prescription dates in this diary for the duration of the registry follow-up, thus, aiding the patient in answering ProClinica™'s questions regarding concomitant medication use since the last follow-up. This patient diary will not be sent back to the Sponsor or the HCP, but will remain the property of the patient; its purpose is solely to assist patients in answering ProClinica™'s questions during these follow-up telephone calls. For patients attending the follow-up visits at hospital (or out-patient treatment) discharge and at between three to five weeks after hospital (or out-patient treatment) discharge, the patient's concomitant medication use data will be recorded on the follow-up CRF by the HCP. If the patient reports any AEs, SAEs or AESIs to ProClinica™ during one of these follow-up telephone calls, a form will be sent to the patient's HCP for confirmation of the reported AE/SAE/AESI and the relevant safety management process will be followed.

	Patients will be considered lost to follow-up if patient follow-up information has not been entered into the registry within 3 months of the date of Eurartesim™ initiation. Reasons for loss to follow-up (e.g. patient not contactable) will be documented.
Scientific Committee	A clinical advisory board (CAB) will be created, constituted of selected local country Key Opinion Leaders (cardiologists and malariologists) plus an expert in pharmacovigilance and a statistician, and will act as a scientific advisory board to review and provide guidance on the registry procedures. This CAB will meet at regular, pre-defined time-points. The main responsibility will be monitoring of safety and enrolment rate. If the latter is far from expectations, a corrective action plan will be finalised, in agreement with the Sponsor and EMA. A Charter will be in place to define the roles, responsibilities and procedures in more details.
Number of patients Number of HCPs Number of countries	300 patients. 15 HCPs. 7 European countries: Belgium, France, Germany, Italy, The Netherlands, Spain and the UK.
Selection criteria	**Inclusion criteria:** The following patients will be included in the registry: - Diagnosed with malaria (*Plasmodium falciparum*); diagnosis will be clinically and parasitologically confirmed. - Prescribed Eurartesim™ treatment on the day on enrolment. - Have been informed, provide consent to participate in this registry and sign the Informed Consent Form (ICF). **Exclusion criteria:** The following patients must not be included in the registry: - Refuse to participate. - Participating in a clinical trial at the time of inclusion in the registry.
Data collection	**The HCPs will complete the following data on the HCP enrolment form:** - Specialty. - Years in practice. - Geographic location. - Institution type. - Number of malaria patients currently treating. - Telephone and email contact information. **The HCPs will collect the following data from the patients on a CRF:** **At enrolment visit:** - Date of visit. - Date of malaria diagnosis. - Demographic characteristics (age, gender, ethnicity [based on the standard definitions of ethnicity used in the EU country where the patient is enrolled in the registry]). - Lifestyle data (smoking status [never/past/current], alcohol consumption [weekly units]). - Physical examination (height, weight). - Relevant medical history and co-morbidities (specifying any cardiac co-morbidities, e.g. ischemic heart disease, heart failure, cardiac hypertrophy and other cardiovascular diseases). - Previous medication use in the past 30 days, including any other treatment taken for malaria (including prescription dates).

	- Thin and thick blood smears for parasite speciation and count. - Routine laboratory data (haematology and biochemistry evaluations, and urinalysis results). - ECG recording(s), as soon as possible and preferably before Eurartesim™ initiation (QTc value, date and time, reason for ECG). **After the patient's full course of Eurartesim™ administration, i.e. at hospital discharge if the patient is hospitalised until the end of their Eurartesim™ administration, or after the patient's full course of Eurartesim™ administration if the patient is discharged early or treated as an out-patient (e.g. at day 3):** - Date of discharge. - Physical examination (height, weight). - Time of Eurartesim™ administration (each of the three days of treatment). - Concomitant medication use since the enrolment visit, including any other treatment taken for malaria and any rescue treatment (including prescription dates). - Time of food intake (for each of the three days of treatment with Eurartesim™). - Thin and thick blood smears for parasite speciation and count (to be taken daily for the duration of the hospitalisation/out-patient visits). - Routine laboratory data (haematology and biochemistry evaluations, and urinalysis results). - ECG recording(s), if deemed clinically appropriate (QTc value, date and time, reason for ECG [e.g. scheduled ECG, occurrence of AESIs, rescue treatment]). - Any AEs/SAEs/AESIs during hospitalisation (or out-patient visits). - Patient status. **According to standard practice, a follow-up visit is recommended between three and five weeks after hospital (or out-patient treatment) discharge:** - Date of the visit. - Physical examination (height, weight). - Concomitant medication use since hospital (or out-patient treatment) discharge, including any other treatment taken for malaria and any rescue treatment (including prescription dates). - Thin and thick blood smears for parasite speciation and count. - Routine laboratory data (haematology and biochemistry evaluations, and urinalysis results). - ECG recording(s), if deemed clinically appropriate (QTc value, date and time, reason for ECG [e.g. scheduled ECG, occurrence of AESIs, rescue treatment]). - Any AEs/SAEs/AESIs since hospital (or out-patient treatment) discharge. - Patient status. ***At telephone follow-up – 15 days after initiation of Eurartesim™ treatment (only conducted if follow-up visit at hospital [or out-patient treatment] discharge is not completed) and 45 days after initiation of Eurartesim™ treatment (only conducted if follow-up visit at three to five weeks after hospital [or out-patient treatment] discharge is not completed):*** - Date of the telephone call. - Concomitant medication use since last follow-up, including any other treatment taken for malaria (including prescription dates). - Any AEs/SAEs/AESIs since last follow-up.

	- Patient status.
Statistical Methods	**Sample size** The sample size has been based mainly on feasibility considerations. According to the WHO/CISID database (http://data.euro.who.int/cisid/?TabID= 279133), during 2007 there were 6,174 reported cases of *Plasmodium falciparum* malaria across the seven European countries included in this registry; Belgium, France, Germany, Italy, The Netherlands, Spain and the UK. Assuming that 5% of these cases are treated with Eurartesim™, there should be approximately 300 potentially eligible patients for inclusion in this registry each year. Thus, when also considering reasons for non-inclusion, such as the patient not willing to participate, it is feasible that this registry will enrol 300 malaria patients treated with Eurartesim™ over the planned 3 year recruitment period. This sample size will ensure a satisfactory level of accuracy to study the association between safety parameters (in particular QTc prolongation) and determinant factors, including age, gender, ethnicity, food intake (time), concomitant medications and co-morbidities. With a sample size of 300 patients, the linear regression test for the correlation coefficient (ρ) for one normally distributed covariate will have a power exceeding 90% (α=0.05, 2-sided) to detect a ρ as low as 0.2. This sample size would allow correction for multiplicity of testing. For example, using the Bonferroni technique, a power of 90% will be preserved for detecting ρ = 0.3 with 50 different covariates (α=0.001, 2-sided). As ECG recordings will only be conducted when deemed clinically appropriate by the patient's HCP (as this is not an interventional study) and there is no previous data regarding Eurartesim™ utilization in European hospitals, it is not possible to anticipate the exact number of patients for whom ECG recordings will be conducted both before Eurartesim™ initiation (i.e. at baseline) and at day 3 following Eurartesim™ administration. With a sample of 200 patients, or 100 patients, and keeping the other assumptions unchanged, the power will be approximately 90% to detect a ρ of approximately 0.25 or 0.30, respectively. In accordance with the secondary objectives of this registry, with 300 patients there is a 90% probability of observing at least one AESI, assuming an overall true incidence of these events of 0.008. Additionally, 300 patients are sufficient to estimate, with a 95% confidence interval and acceptable precision (2.6%) a true incidence of any AEs or other abnormalities (e.g. QTc prolongation) of approximately 5%. The registry will be closed to new entries once the number of 300 patients having validated data has been reached. The closure will be in agreement with the EMA. **Statistical Analysis** Statistical analyses will be carried out using SAS software version 9.2. REGISTRAT-MAPI will develop a statistical analysis plan to be reviewed by Sigma-Tau and the CAB. This statistical analysis plan will include statistical methods, population definitions, output specifications and data definition tables. On an annual basis, interim analyses will be conducted and tables and listings (cumulative data) will be produced to enable the reporting of key interim outcomes to regulatory authorities and the CAB. 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. If patients are lost to follow-up, any data collected up to that point (including any

	adverse event data, e.g. QTc prolongation) will be included in the statistical analyses (including analysis of the adverse event outcome, e.g. QTc prolongation) **Description of the registry 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 (i.e. specialty, years in practice, geographic location, institution type, number of malaria patients currently treating). - Patients: From the details recorded in the patient log, the proportion of patients actually included in the registry will also be described; the denominator will be the total number of patients asked to participate. This analysis will enable assessment of the overall representativeness of the included registry population compared to patients not participating in the registry. Two main populations will be considered in the statistical analysis: - All patients included in the registry, having taken at least one dose of Eurartesim™ treatment (Safety Population). - All patients having an ECG recording at baseline, i.e. before Eurartesim™ initiation, and at day 3, i.e. following the last Eurartesim™ dose intake (QTc Population). Both populations (i.e. Safety Population and QTc Population) will be described according to demographic characteristics (e.g. age, gender, ethnicity). **Response to the main objective** In accordance with the primary objective of this registry, the main focus of the statistical analysis will be the assessment of the association between safety parameters (in particular QTc prolongation) and determinant factors, including age, gender, ethnicity, lifestyle (smoking status, alcohol consumption), food intake (time), concomitant medications and co-morbidities. For QTc prolongation (Fridericia correction) and relevant laboratory variables, this relationship will be assessed via regression analysis. The response variable will be the change in the QTc value between the baseline and day 3 assessments for each patient. Different transformations will be used to normalize the data, if required; factors will be entered into the regression model as dummy variables. This analysis will be conducted on the QTc Population for the QTc variable and on the Safety Population for the laboratory variables. For AEs (Y/N), this relationship will be assessed via logistic regression. The same analysis will be repeated for the AESIs, depending on their frequency. These analyses will be conducted on the Safety Population. The relationship between any AESIs and QTc prolongation will also be assessed. **Response to the secondary objectives** A descriptive analysis of QTc data (absolute values and changes from baseline to day 3) using both Bazett (QTcB) and Fridericia (QTcF) corrections, as well as the laboratory variables, will be conducted.

	Descriptive statistics relating to the basic efficacy data (i.e. parasite count, time to parasite clearance) will also be presented. The proportion of patients with an ECG recording for each day of Eurartesim™ intake (e.g. day 1, day 2, day 3) will be presented, both overall and by reason for the ECG recording. The incidence of all and each individual AESI following Eurartesim™ initiation will be calculated. The incidence of all AEs and SAEs, including neurotoxicity and phototoxicity, following Eurartesim™ initiation will also be estimated. Incidences of cardiac events, AESIs, AEs and SAEs will be presented overall (taking into account all of the standard ways of summarizing these data, i.e. by MedDRA System Organ Class, severity, etc…) as well as by age, gender, ethnicity, food intake (time), concomitant medications and co-morbidities. The incidence of patients with reported QTc abnormalities (e.g. QTc prolongation) following Eurartesim™ initiation will be estimated. Incidence of abnormal laboratory data (haematology and biochemistry evaluations, and urinalysis results), with respect to the normality ranges, will also be calculated. All of the analyses described above will be conducted on the Safety Population, with the exception of those analyses concerning QTc abnormalities, which will be based on the QTc Population. Incidence will be generated based on the total number of unique patients with a first diagnosis of the variable under study (numerator) divided by the total person-years at risk of the variable under study (denominator). 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 patients who discontinue the registry prematurely, a sensitivity analysis will be performed considering all patients, assuming that patients who discontinued the registry had experienced AESIs; this will provide us with the highest estimation of AESI occurrence (i.e. the worst-case scenario). Finally, narratives of all SAEs and AESIs will be compiled. **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 between subgroups 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: July 2012 Last patient in: April 2015 Database lock: July 2015 Final Clinical Study Report: October 2015

2. REGISTRY RATIONALE

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” (WHO, 2008).

Eurartesim™ (dihydroartemisinin [DHA] - piperaquine [PQP]) is an artemisinin-based combination therapy (ACT), which involves the simultaneous use of two 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 (WHO, 2010).

Substantial data are available regarding the effects of the active substances of Eurartesim™ (DHA and PQP) alone or in combination in patients (Sigma-Tau, 2009). In adults, the most common side-effects observed with Eurartesim™ use (seen in 1-10 patients in 100) are anaemia, headache, QTc (corrected QT segment length) prolongation, tachycardia, asthenia and pyrexia. In children, the most common side-effects observed with Eurartesim™ use (seen in >1 patient in 10) are influenza, cough and pyrexia (EMA, 2011a).

Potential QTc prolongation

In pre-clinical studies, electrocardiographic (ECG) effects have been observed, including prolongation of QTc with noted ST-T segment changes in rats and dogs given arteether (Brewer *et al*, 1994a; Brewer *et al*, 1994b; Classen *et al*, 1999).

In dogs given intravenous artesunate (50mg/kg/day) for 14 days, no clinical observations or ECG changes were observed. Yet, cardiovascular sinus bradycardia and a reversible prolongation of the QTc interval have been reported following artesunate exposure (Chalker *et al*, 1990).

Acute cardiovascular toxicity of PQP in rabbits was compared with that of chloroquine (another anti-malarial) by determining the intravenous dose that caused ECG abnormalities. Using this determination, it was observed that, in general, PQP had a better cardiovascular toxicity profile than chloroquine. Prolongation of the PR and QRS duration was commonly observed with PQP at a 5-fold higher cumulative dose of 50-56mg/kg of PQP compared with 9-11mg/kg of chloroquine. Atrioventricular block was present in 100% of rabbits after a cumulative chloroquine dose of 19mg/kg, whereas only 2 rabbits showed this effect with PQP (Davis *et al*, 2005).

As a result of the above data, Sigma-Tau specifically monitored QTc prolongation in their clinical trials.

ECGs were taken on days 0, 2 and 7 after Eurartesim™ initiation. The QTc prolongation potential was analysed according to the ICH E14 guideline (ICH, 2005). The analyses showed that (Sigma-Tau, 2010):

- At baseline, QTc prolongation is associated with the malaria infection state.
- On day 2, a higher proportion of patients with borderline and prolonged QTc values were present in the DHA/PPQ group than the comparator groups.

- By day 7, differences in the proportions of patients with borderline and prolonged QTc had resolved.
- Only 3 patients (0.39%) had a QTc>500msec (QTcF) on day 2 in the Asian phase III study.
- This short-term QTc prolongation does not translate into a tangible risk of suffering clinically significant treatment emergent adverse events that are known to be associated with QTc interval prolongation.

ECG findings suggested that Eurartesim™ does not cause clinically relevant cardiotoxicity. The QTc prolongation observed was comparable with that observed with other anti-malarials, including drugs with no known cardiac effects (Sigma-Tau, 2009).

A further study addressing the potential QTc prolongation of Eurartesim™ demonstrated that this prolongation is significantly reduced when Eurartesim™ is administered in fasting conditions with water (Sigma-Tau, 2010). The potential for Eurartesim™ to prolong the QTc interval was investigated in parallel groups of healthy volunteers who took each dose of Eurartesim™ with either high-fat/high-Kcal (~1,000 Kcal) or high-fat/low-Kcal (~400 Kcal) fat/calorie meals or in fasting conditions. Compared to placebo, the maximum mean increases in QTc on day 3 of dosing with Eurartesim™ were 45.2, 35.5 and 21.0msec under the respective dosing conditions. The QTc prolongation observed under fasting conditions lasted between 4 and 11 hours after the last dose was administered on day 3. The mean QTc prolongation compared to placebo decreased to 11.8msec at 24 hours and to 7.5msec at 48 hours. No healthy subject dosed in fasting conditions showed a QTc greater than 480msec or an increase over baseline greater than 60msec. The number of subjects with QTc greater than 480msec after dosing with low fat meals was 3/64, while 10/64 had QTc values over this threshold after dosing with high fat meals. No subject had a QTc value greater than 500msec in any of the dosing conditions (EMA, 2011b).

Data indicate that co-administration of Eurartesim™ with fat increases the bio-availability of PQP and possibly also the efficacy, which may increase its effect on the QTc interval (Price, Dorsey and Nosten, 2009).

Due to this potential for QTc prolongation, the Summary of Product Characteristics (SmPC) states that Eurartesim™ should be administered with water but without food and at least three hours from any meal (EMA, 2011a).

Rationale for this registry

Marketing authorisation for Eurartesim™ was obtained on 27th October 2011. Launch of Eurartesim™ in eight European countries is expected in June 2012.

Eurartesim™ is administered as a single daily dose for three days; patients are generally hospitalised for the duration of their Eurartesim™ treatment, but may be treated on an out-patient basis if they refuse hospitalisation.

Due to the clinical trial data presented above, the Eurartesim™ product information (SmPC) states that Eurartesim™ should not be prescribed to patients with a history of cardiovascular diseases, or taking any cardiovascular medication, due to the potential for QTc prolongation of Eurartesim™ and serious cardiac events that are associated with QTc prolongation (EMA, 2011a).

The European Medicines Agency (EMA) has requested Sigma-Tau to perform a post-authorisation safety study (PASS) in order to further assess the potential for cardiotoxicity and QTc prolongation following Eurartesim™ exposure and to identify and quantify the unknown risks associated with the use of any new chemical entity. Thus, this registry is an essential component of the ongoing assessment of the safety of Eurartesim™. Through the registry, patients exposed to Eurartesim™ for the treatment of malaria will be registered by

healthcare providers (HCPs) and any AEs/SAEs/AESIs recorded. This information will be used to detect any potential safety risks to patients exposed to Eurartesim™ for the treatment of malaria.

This protocol details strategy considerations for a safety registry in Europe for patients exposed to Eurartesim™ for the treatment of malaria.

3. REGISTRY OBJECTIVES

The primary objective is to:

- Study the association between safety parameters (in particular QTc prolongation) and the following factors:
  - Age.
  - Gender.
  - Ethnicity.
  - Lifestyle (smoking status, alcohol consumption).
  - Food intake (time).
  - Co-morbidities.
  - Co-medications.

The secondary objectives are to:

- Estimate the incidence of QTc prolongation following Eurartesim™ initiation.
- Estimate the incidence of all and each individual pre-specified treatment-emergent adverse events of special interest (AESI) following Eurartesim™ initiation. The following events are defined as AESIs:
  - Torsade de Pointes (TdP).
  - Sudden death.
  - Ventricular tachycardia.
  - Ventricular fibrillation and flutter.
  - Syncope.
  - Seizures.
  - Sustained arrhythmias (repetitive or lasting >30 sec at a ventricular rate >120 bpm).
- Estimate the incidence of all adverse events (AEs) and serious adverse events (SAEs) following Eurartesim™ initiation, including neurotoxicity and phototoxicity.
- Assess the relationship between QTc prolongation and the AESIs, AEs and SAEs.

4. METHODOLOGY

4.1 Registry design

A multi-centre safety registry for malaria patients treated with Eurartesim™ will be conducted in seven European Countries; Belgium, France, Germany, Italy, The Netherlands, Spain and the UK.

This is an observational, non-comparative, non-interventional longitudinal study. As an observational study, this will not change the patient-HCP relationship, nor influence the HCP's drug prescription or therapeutic management of the patient.

HCPs will include all patients meeting the inclusion criteria and agreeing to take part in the registry. Paediatric patients (<18 years of age) may also be enrolled for inclusion in the registry. If a paediatric patient is enrolled, the child's parent must provide informed consent for their child's data to be collected and provide follow-up contact information to ProClinica™.

Diagnosis of malaria (*Plasmodium falciparum*) will be clinically and parasitologically confirmed.

Follow-up visits will take place according to routine clinical practice, at hospital (or out-patient treatment) discharge following Eurartesim™ treatment and 3 to 5 weeks after hospital (or out-patient treatment) discharge (refer to Table 1).

ECG recordings, with special attention to the QTc measurement, will be taken based on the recommendations specified in the SmPC for Eurartesim™ (EMA, 2011b) (refer to Section 4.5.3). ECG recordings will only be conducted when deemed clinically appropriate by the patient's HCP, as this is not an interventional study.

FIGURE 1: REGISTRY DIAGRAM

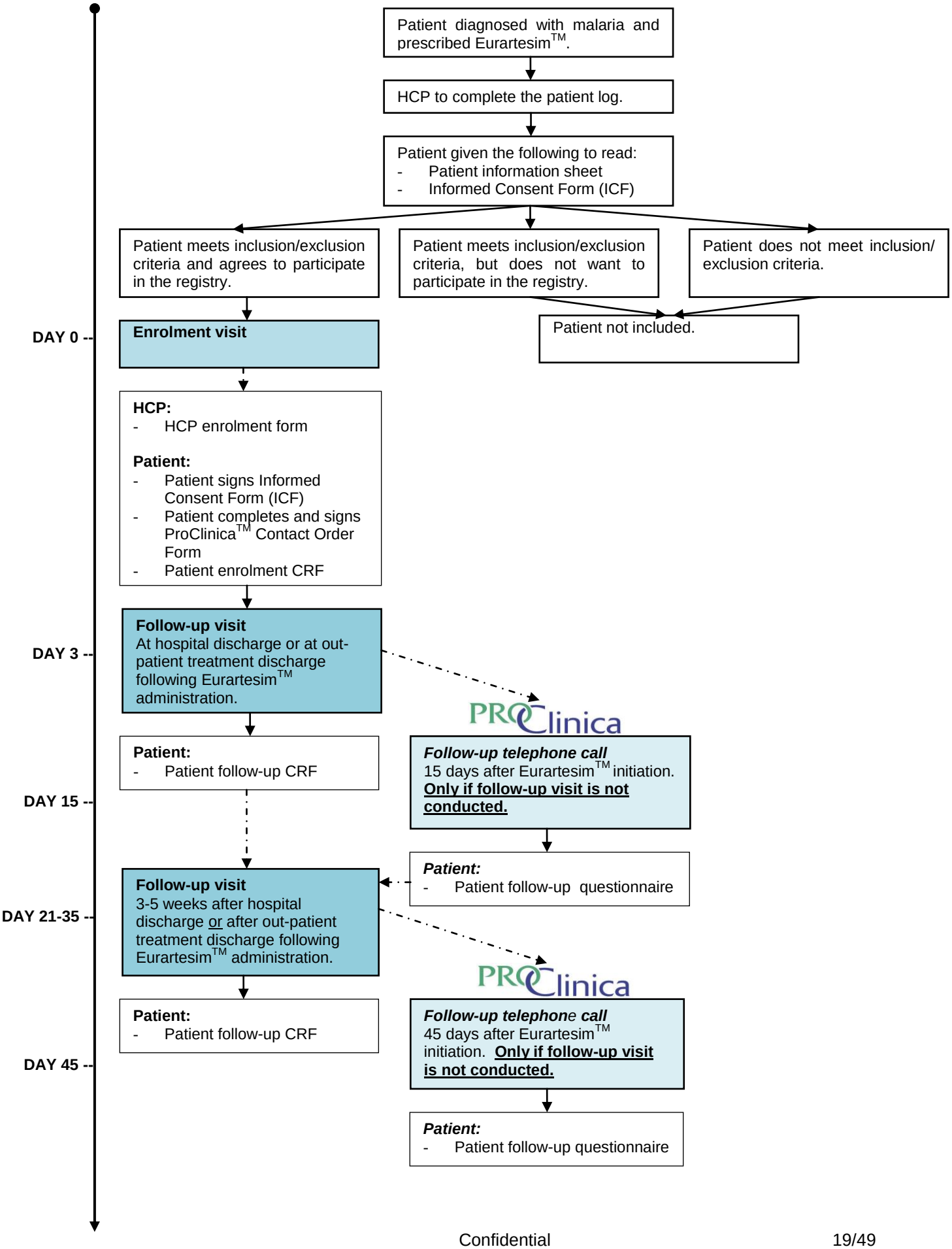

TABLE 1: SCHEDULE OF REGISTRY ASSESSMENTS

Assessment by HCPs	**Visit 1 (Enrolment)**	**Visit 2 (Hospital discharge or out-patient treatment discharge)**	**Telephone Call 1 (15 days after Eurartesim™ initiation - only conducted if Visit 2 not completed)**	**Visit 3 (3 to 5 weeks after hospital discharge or out-patient treatment discharge)**	**Telephone Call 2 (45 days after Eurartesim™ initiation - only conducted if Visit 3 not completed)**
Date of visit/telephone call	**x**	**x**	**x**	**x**	**x**
Date of malaria diagnosis	**x**				
Demographic characteristics	**x**				
Lifestyle data	**x**				
Physical examination	**x**	**x**		**x**	
Relevant medical history and co-morbidities (specifying any cardiac co-morbidities)	**x**				
Concomitant medication use	**x**	**x**	**x**	**x**	**x**
Thin and thick blood smears	**x**	**x***		**x**	
Routine laboratory data	**x**	**x***		**x**	
Time of Eurartesim™ administration		**x**			
Food intake (time)		**x**			
ECG recordings		**x***		**x**	
AEs/SAEs/AESIs		**x**	**x**	**x**	**x**
Patient status		**x**	**x**	**x**	**x**

* All tests and ECGs performed during the hospitalisation or out-patient treatment should be recorded (not only those performed on the day of discharge).

4.2 Selection criteria

Inclusion Criteria:

The following patients will be included in the registry:

- Diagnosed with malaria (*Plasmodium falciparum*); diagnosis will be clinically and parasitologically confirmed.
- Prescribed Eurartesim™ treatment on the day on enrolment.
- Have been informed, provide consent to participate in this registry and sign the Informed Consent Form (ICF).

Exclusion criteria:

The following patients must not be included in the registry:

- Refuse to participate.
- Participating in a clinical trial at the time of inclusion in the registry.

4.3 HCP selection

4.3.1 Type of HCPs

Health Care Providers (HCPs) known to treat and follow-up malaria patients will be contacted for inclusion as investigators into the registry.

Malaria patients who are not part of one of the selected sites will be able to contact their hospital HCP who will contact the Sponsor on their behalf in order to be included in the registry. Patients will be made aware of the registry via the educational outreach program, including the Patient Information Sheet included with the Eurartesim™ packaging (refer to Section 4.3.2).

4.3.2 Educational outreach program

An educational ‘outreach program’ will be implemented to raise awareness of the registry among both patients and HCPs, and increase both patient and HCP participation.

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

- 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.

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 websites (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.

4.3.3 Sampling

REGISTRAT-MAPI is also conducting a 'Pregnancy Registry for Eurartesim™' registry on behalf of Sigma-Tau in 57 sites across the same seven European Countries as this registry is to be conducted; Belgium, France, Germany, Italy, The Netherlands, Spain and the UK.

These sites will be contacted by telephone by local language Epidemiologic Research Associates (ERAs), in order to present the registry and its process in detail, and to determine if they agree to participate in the safety registry. This telephone call will be based on a pre-defined standardised call-script, translated into local language. The site selection process will end as soon as 15 sites with eligible patients agree to participate in the safety registry. The site selection process will ensure that the included sites are distributed over the participating European countries in order to minimise any country effect.

From these 15 sites, 300 malaria patients treated with Eurartesim™ will be recruited sequentially for enrolment into this registry.

During patient enrolment, REGISTRAT-MAPI will provide Sigma-Tau with data on current recruitment rates. This will include tables with the numbers of active sites, enrolled patients and completed patients. If analyses show that recruitment rates are lower than anticipated/required, an action plan will be finalised, in agreement with Sigma-Tau and the CAB, to further increase the number of study sites.

4.4 Sample size calculation

The sample size has been based mainly on feasibility considerations. According to the WHO/CISID database (http://data.euro.who.int/cisid/?TabID= 279133), during 2007 there were 6,174 reported cases of *Plasmodium falciparum* malaria across the seven European countries included in this registry; Belgium, France, Germany, Italy, The Netherlands, Spain and the UK (WHO/CISID, 2011). Assuming that 5% of these cases are treated with Eurartesim™, there should be approximately 300 potentially eligible patients for inclusion in this registry each year. Thus, when also considering reasons for non-inclusion, such as the patient not willing to participate, it is feasible that this registry will enrol 300 malaria patients treated with Eurartesim™ over the planned 3 year recruitment period.

This sample size will ensure a satisfactory level of accuracy to study the association between safety parameters (in particular QTc prolongation) and determinant factors, including age, gender, ethnicity, food intake (time), concomitant medications and co-morbidities.

With a sample size of 300 patients, the linear regression test for the correlation coefficient (ρ) for one normally distributed covariate will have a power exceeding 90% (α=0.05, 2-sided) to detect a ρ as low as 0.2. This sample size would allow correction for multiplicity of testing. For example, using the Bonferroni technique, a power of 90% will be preserved for detecting ρ = 0.3 with 50 different covariates (α=0.001, 2-sided).

As ECG recordings will only be conducted when deemed clinically appropriate by the patient's HCP (as this is not an interventional study) and there is no previous data regarding Eurartesim™ utilization in European hospitals, it is not possible to anticipate the exact number of patients for whom ECG recordings will be conducted both before Eurartesim™ initiation (i.e. at baseline) and at day 3 following Eurartesim™ administration. With a sample of 200 patients, or 100 patients, and keeping the other assumptions unchanged, the power will be approximately 90% to detect a ρ of approximately 0.25 or 0.30, respectively.

In accordance with the secondary objectives of this registry, with 300 patients there is a 90% probability of observing at least one AESI (i.e. TdP, sudden cardiac death, ventricular tachycardia, ventricular fibrillation and flutter, syncope, seizures, sustained arrhythmias [repetitive or lasting >30 sec at a ventricular rate of >120 bpm]), assuming an overall true incidence of these events of 0.008, as described below:

- Prevalence of congenital long-QT syndrome (i.e. TdP) is 0.0002 (Schwartz *et al*, 2009).
- Incidence of sudden cardiac death is 0.0015 (ESC, 2006).
- Incidence of ventricular fibrillation is 0.0012 (Medscape, 2011).
- Incidence of syncope is 0.003 (Soteriades *et al*, 2002), with a sharp rise after the age of 70 years (ESC, 2009).
- Atrial fibrillation is the most common type of sustained arrhythmia. Prevalence is less than 0.01 in people under 60 years of age, with a rise after the age of 80 years (Thrombosis Adviser, 2011).
- The incidence and prevalence of ventricular tachycardia is difficult to determine because of the lack of symptoms when it is non-sustained (Medical Disability Advisor, 2011).

In addition, 300 patients are sufficient to estimate, with a 95% confidence interval and acceptable precision (2.6%) a true incidence of any AEs or other abnormalities (e.g. QTc prolongation) of approximately 5%.

The registry will be closed to new entries once the number of 300 patients having validated data has been reached. The closure will be in agreement with the EMA.

4.5 Data collected

REGISTRAT-MAPI EU will develop a formalised CRF (Case Report Form) for data collection purposes.

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

4.5.1 From the investigator

The HCPs will complete an HCP enrolment form, collecting the following data:

- Specialty.
- Years in practice.
- Geographic location.
- Institution type.
- Number of malaria patients currently treating.
- Telephone and email contact information.

4.5.2 From the patient

For this registry, the following events are defined as AESIs:

- Torsade de Pointes (TdP).
- Sudden death.
- Ventricular tachycardia.
- Ventricular fibrillation and flutter.
- Syncope.
- Seizures.
- Sustained arrhythmias (repetitive or lasting >30 sec at a ventricular rate >120 bpm).

The HCPs will collect the following data from the patients on a CRF:

At enrolment visit:

- Date of visit.
- Date of malaria diagnosis.
- Demographic characteristics (age, gender, ethnicity [based on the standard definitions of ethnicity used in the EU country where the patient is enrolled in the registry]).
- Lifestyle data (smoking status [never/past/current], alcohol consumption [weekly units]).
- Physical examination (height, weight).
- Relevant medical history and co-morbidities (specifying any cardiac co-morbidities, e.g. ischemic heart disease, heart failure, cardiac hypertrophy and other cardiovascular diseases).
- Previous medication use in the past 30 days, including any other treatment taken for malaria (including prescription dates).
- Thin and thick blood smears for parasite speciation and count.
- Routine laboratory data (haematology and biochemistry evaluations, and urinalysis results).
- ECG recording(s), as soon as possible and preferably before Eurartesim™ initiation (QTc value, date and time, reason for ECG).

After the patient's full course of Eurartesim™ administration, i.e. at hospital discharge if the patient is hospitalised until the end of their Eurartesim™ administration, or after the patient's full course of Eurartesim™ administration if the patient is discharged early or treated as an out-patient (e.g. at day 3):

- Date of discharge.
- Physical examination (height, weight).
- Time of Eurartesim™ administration (each of the three days of treatment).
- Concomitant medication use since the enrolment visit, including any other treatment taken for malaria and any rescue treatment (including prescription dates).
- Time of food intake (for each of the three days of treatment with Eurartesim™).
- Thin and thick blood smears for parasite speciation and count (to be taken daily for the duration of the hospitalisation/out-patient visits).
- Routine laboratory data (haematology and biochemistry evaluations, and urinalysis results).
- ECG recording(s), if deemed clinically appropriate (QTc value, date and time, reason for ECG [e.g. scheduled ECG, occurrence of AESIs, rescue treatment]).
- Any AEs/SAEs/AESIs since the enrolment visit.
- Patient status.

According to standard practice, a follow-up visit is recommended between three and five weeks after hospital (or out-patient treatment) discharge:

- Date of the visit.
- Physical examination (height, weight).

- Concomitant medication use since hospital (or out-patient treatment) discharge, including any other treatment taken for malaria and any rescue treatment (including prescription dates).
- Thin and thick blood smears for parasite speciation and count.
- Routine laboratory data (haematology and biochemistry evaluations, and urinalysis results).
- ECG recording(s), if deemed clinically appropriate (QTc value, date and time, reason for ECG [e.g. scheduled ECG, occurrence of AESIs, rescue treatment]).
- Any AEs/SAEs/AESIs since hospital (or out-patient treatment) discharge.
- Patient status.

At telephone follow-up – 15 days after initiation of Eurartesim™ treatment (only conducted if follow-up visit at hospital [or out-patient treatment] discharge is not completed) and 45 days after initiation of Eurartesim™ treatment (only conducted if follow-up visit at three to five weeks after hospital [or out-patient treatment] discharge is not completed):

- Date of the telephone call.
- Concomitant medication use since last follow-up, including any other treatment taken for malaria (including prescription dates).
- Any AEs/SAEs/AESIs since last follow-up.
- Patient status.

4.5.3 Assessment of ECG recordings

ECG recordings, with special attention to the QTc measurement, will be taken based on the recommendations specified in the SmPC for Eurartesim™ (EMA, 2011b):

- As soon as possible after patient enrolment into the registry (preferably before the first Eurartesim™ dose).
- As early as possible during treatment with Eurartesim™.
- When clinically appropriate, consideration should be given to obtaining an ECG before the last of the three daily doses is taken and approximately 4-6 hours after the last dose, since the risk of QTc interval prolongation may be greatest during this period
- In the occurrence of an AESI.
- If rescue treatment is administered.

ECG recordings should only be conducted when deemed clinically appropriate by the patient's HCP; this is not an interventional study.

For each of the ECGs conducted, the following will be recorded:

- QTc result (absolute value, calculated using Bazett (QTcB) and/or Fridericia (QTcF) corrections [Bazett, 1920; Fridericia, 1920]).
- Date and time of the ECG recording.

- Reason for the ECG (e.g. scheduled ECG, occurrence of AESIs, rescue treatment).

Definitions of normal, borderline and prolonged QTcB and QTcF are reported in Table 2 (Sigma-Tau, 2009).

TABLE 2: DEFINITIONS OF NORMAL, BORDERLINE AND PROLONGED QTcB AND QTcF

	Range of QTcB and QTcF		
	Normal	**Borderline**	**Prolonged**
Adult Males and Children (aged 1 to 12 years)	<430msec	430-450msec	>450msec
Adult Females	<450msec	450-470msec	>470msec

QTc intervals of more than 500msec are associated with a pronounced risk for potentially life-threatening ventricular tachyarrhythmias. Patients found to have a prolongation to this extent should, therefore, have further ECG monitoring during the following 24-48 hours. These patients should not receive another dose of Eurartesim™ and alternative antimalarial therapy should be instituted (EMA, 2011b).

4.6 Data management process

Each document received at REGISTRAT-MAPI will be tracked at reception and stamped.

Data entry of data collection forms is double-blind data entry except for free text (single data entry). All discrepancies detected by the data entry software will be re-entered by the same operators. Remaining discrepancies will be flagged to be treated by the data manager during data management process.

Documents will be filed after data entry by centre and by patient.

Concomitant medications will be coded with the WHODrug. Drug reactions will be coded with MedDRA (the most recent version).

Queries will be edited for the data collection form. Before printing of queries, all detected mistakes will be verified by the data manager. Obvious corrections will be undertaken according to the data handling manual. HCPs will be contacted by telephone in order to solve the remaining mistakes. A copy of the corrections will be faxed to the HCPs for filing in the patient file.

Each query will be tracked after editing and reception. Corrections will be entered by the data manager in charge of the registry and will be filed with the data collection form after data entry. After completion, the edit check program will be re-run to ensure that all erroneous data have been corrected. If not, new queries will be generated and resolved.

On an annual basis, interim database lock and interim statistical analysis will be conducted (cumulative data).

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

4.7 Statistical analysis

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

REGISTRAT-MAPI will develop a statistical analysis plan to be reviewed by Sigma-Tau and the CAB. This statistical analysis plan will include statistical methods, population definitions, output specifications and data definition tables.

On an annual basis, interim analyses will be conducted and tables and listings (cumulative data) will be produced to enable the reporting of key interim outcomes to regulatory authorities and the CAB.

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.

If patients are lost to follow-up, any data collected up to that point (including any adverse event data, e.g. QTc prolongation) will be included in the statistical analyses (including analysis of the adverse event outcome, e.g. QTc prolongation)

Description of the registry 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 (i.e. specialty, years in practice, geographic location, institution type, number of malaria patients currently treating).

- Patients:

From the details recorded in the patient log (refer to Section 5.2), the proportion of patients actually included in the registry will also be described; the denominator will be the total number of patients asked to participate. This analysis will enable assessment of the overall representativeness of the included registry population compared to patients not participating in the registry.

Two main populations will be considered in the statistical analysis:

- All patients included in the registry, having taken at least one dose of Eurartesim™ treatment (Safety Population).
- All patients having an ECG recording at baseline, i.e. before Eurartesim™ initiation, and at day 3, i.e. following the last Eurartesim™ dose intake (QTc Population).

Both populations (i.e. Safety Population and QTc Population) will be described according to demographic characteristics (e.g. age, gender, ethnicity).

Response to the main objective

In accordance with the primary objective of this registry, the main focus of the statistical analysis will be the assessment of the association between safety parameters (in particular QTc prolongation) and the following factors:

- Age.
- Gender.

- Ethnicity.
- Lifestyle (smoking status, alcohol consumption).Food intake (time).
- Concomitant medications.
- Co-morbidities.

For QTc prolongation (Fridericia correction) and relevant laboratory variables, this relationship will be assessed via regression analysis. The response variable will be the change in the QTc value between the baseline and day 3 assessments for each patient. Different transformations will be used to normalize the data, if required; factors will be entered into the regression model as dummy variables. This analysis will be conducted on the QTc Population for the QTc variable and on the Safety Population for the laboratory variables.

For AEs (Y/N), this relationship will be assessed via logistic regression. The same analysis will be repeated for the AESIs, depending on their frequency. These analyses will be conducted on the Safety Population.

The relationship between any AESIs and QTc prolongation will also be assessed.

Response to the secondary objectives

A descriptive analysis of QTc data (absolute values and changes from baseline to day 3) using both Bazett (QTcB) and Fridericia (QTcF) corrections (Bazett, 1920; Fridericia, 1920), as well as the laboratory variables, will be conducted.

Descriptive statistics relating to the basic efficacy data (i.e. parasite count, time to parasite clearance) will also be presented.

The proportion of patients with an ECG recording for each day of Eurartesim™ intake (e.g. day 1, day 2, day 3) will be presented, both overall and by reason for the ECG recording.

The incidence of all and each individual AESI following Eurartesim™ initiation will be calculated. The following events will be defined as AESIs:

- Torsade de Pointes (TdP).
- Sudden death.
- Ventricular tachycardia.
- Ventricular fibrillation and flutter.
- Syncope.
- Seizures.
- Sustained arrhythmias (repetitive or lasting >30 sec at a ventricular rate >120 bpm).

The incidence of all AEs and SAEs, including neurotoxicity and phototoxicity, following Eurartesim™ initiation will also be estimated.

Incidences of cardiac events, AESIs, AEs and SAEs will be presented overall (taking into account all of the standard ways of summarizing these data, i.e. by MedDRA System Organ Class, severity, etc…) as well as by age, gender, ethnicity, food intake (time), concomitant medications and co-morbidities.

The incidence of patients with reported QTc abnormalities (e.g. QTc prolongation [refer to Section 4.5.3]) following Eurartesim™ initiation will be estimated.

Incidence of abnormal laboratory data (haematology and biochemistry evaluations, and urinalysis results), with respect to the normality ranges, will also be calculated.

All of the analyses described above will be conducted on the Safety Population, with the exception of those analyses concerning QTc abnormalities which will be based on the QTc Population.

Incidence will be generated based on the total number of unique patients with a first diagnosis of the variable under study (numerator) divided by the total person-years at risk of the variable under study (denominator). 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 patients who discontinue the registry prematurely, a sensitivity analysis will be performed considering all patients, assuming that patients who discontinued the registry had experienced AESIs; this will provide us with the highest estimation of AESI occurrence (i.e. the worst-case scenario).

Finally, narratives of all SAEs and AESIs will be compiled.

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 between subgroups 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%.

5. REGISTRY CONDUCT

5.1 Site initiation

A study kit will be sent to each identified/selected HCP at registry initiation once all the necessary administrative procedures have been completed (i.e. confidentiality agreement, financial agreement, CV,… where applicable).

The study kit contains the following:

- Registry protocol.
- HCP enrolment form.
- Patient log.
- Patient information sheet and Informed Consent Forms (ICFs).
- Patient Contact Order Form (COF).
- Baseline and follow-up Case Report Forms (CRFs).
- Pre-paid envelopes.
- Patient concomitant medication use diary.

On reception of the study kit, an initiation phone call will be organised by an ERA to review the registry, and explain the protocol, CRF and completion guidelines, data collection and practical (i.e. logistic and administrative) aspects of the registry. The ERA will also address any issues and validate site participation. A written report will be documented for each call.

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

5.2 Patients' inclusion

During the patient inclusion phase, HCPs will be asked to report all screened patients presenting for consultation in the patient log. This patient log will contain no patient identifiers; minimum data will be collected, such as patient age, gender and ethnicity. This patient log will, therefore, list all patients diagnosed with malaria and prescribed Eurartesim™ whether they accept to participate in the registry or not and will enable assessment of the overall representativeness of the included registry population compared to patients not participating in the registry.

Patient status will be recorded at each visit/telephone call in order to collect data on the enrolment status of the patient and, if applicable, the reason for premature discontinuation of the registry (e.g. patient no longer wishes to participate, moved away, lost to follow-up).

HCPs will each be asked to include all patients meeting the eligibility criteria and agreeing to take part in the registry (300 patients in total).

During the recruitment phase, and for each patient, the HCP will:

- Explain the registry to the patient (in particular the objectives of the registry).
- Give him/her a patient information sheet and Informed Consent Form (ICF) and ask the patient to read and sign it to confirm his/her agreement to participate in the registry.
- Complete the enrolment CRF (to be posted to REGISTRAT-MAPI).
- Explain the role of ProClinica™ to the patient and ask the patient to complete and sign a Contact Order Form (COF) (to be faxed to ProClinica™).
- Give the patient a concomitant medication use diary and ask the patient to complete this (i.e. medication names and prescription dates) for the duration of the registry follow-up.

Before any procedure associated with the registry is carried out, the patient information and Informed Consent Form (ICF) should be signed and dated by the patient.

The COF will also ask HCPs to provide the expected date of Eurartesim™ initiation. Thus, enabling ProClinica™ (refer to Section 5.4) to contact the participating patients for follow-up by telephone after 15 days following Eurartesim™ initiation should the follow-up visit at hospital (or out-patient treatment) discharge not be completed, and 45 days following Eurartesim™ initiation should the follow-up visit at three to five weeks after hospital (or out-patient treatment) discharge not be completed.

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

The registry will be closed to new entries once 300 patients with validated data have been enrolled. This closure will be in agreement with the EMA.

5.3 Follow-up

Data will be collected during the normal course of patient care.

According to routine clinical practice, most patients receiving Eurartesim™ for the treatment of malaria will be hospitalised for at least three days and follow-up (including the recording of ECG and blood withdrawing results) will be conducted at hospital discharge. For the minority of patients who refuse hospitalisation, follow-up (including the recording of ECG and blood withdrawing results) will be performed on an out-patient basis and the patients will be asked to contact their HCP with these test results, in order for the data to be recorded on the CRF. A follow-up visit is also recommended between three to five weeks after hospital (or out-patient treatment) discharge.

During the follow-up visits, the HCP will:

- Complete a follow-up CRF.
- Post the follow-up CRF to REGISTRAT-MAPI in the pre-paid envelope, following the visit.

Patients will remain in the registry even if a follow-up visit is not performed. It is anticipated that some patients may not attend the follow-up visit at three to five weeks after hospital (or out-patient treatment) discharge.

ProClinica™ (refer to Section 5.4) will contact the participating patients for follow-up by telephone after 15 days following Eurartesim™ initiation should the follow-up visit at hospital (or out-patient treatment) discharge not be completed, and 45 days following Eurartesim™ initiation should the follow-up visit at three to five weeks after hospital (or out-patient treatment) discharge not be completed. Patients will be flagged for telephone follow-up by ProClinica™ if their corresponding CRF has not been received after 15 days and 45 days, respectively.

During these follow-up telephone calls, ProClinia™ will collect data regarding:

- Concomitant medication use since last follow-up, including any other treatment taken for malaria (including prescription dates).
- Any AEs/SAEs/AESIs since last follow-up.
- Patient status.

In order to aid patient recall of concomitant medication use since the last follow-up (i.e. medication names and prescription dates) and enhance the reliability of the concomitant medication use data collection during these follow-up telephone calls, a patient diary will be employed. At the registry enrolment visit, all patients will receive a diary and be asked to record the names of any medications used and the prescription dates in this diary for the duration of the registry follow-up, thus, aiding the patient in answering ProClinica™'s questions regarding concomitant medication use since the last follow-up. This patient diary will not be sent back to the Sponsor or the HCP, but will remain the property of the patient; its purpose is solely to assist patients in answering ProClinica™'s questions during these follow-up telephone calls. For patients attending the follow-up visits at hospital (or out-patient treatment) discharge and at between three to five weeks after hospital (or out-patient treatment) discharge, the patient's concomitant medication use data will be recorded on the follow-up CRF by the HCP.

If the patient reports any AEs, SAEs or AESIs to ProClinica™ during one of these follow-up telephone calls, a form will be sent to the patient's HCP for confirmation of the reported AE/SAE/AESI and the relevant safety management process will be followed (refer to Section 7).

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

Patients will be considered lost to follow-up if patient follow-up information has not been entered into the registry within 3 months of the date of Eurartesim™ initiation. Reasons for loss to follow-up (e.g. patient not contactable) will be documented.

5.4 Organisation around data collection

Recruitment and monitoring of HCPs will be handled by REGISTRAT-MAPI on behalf of Sigma Tau. All contacts with HCPs will be carried out by REGISTRAT-MAPI.

Management of direct patients contacts will be undertaken by a dedicated and REGISTRAT-MAPI independent unit, ProClinica™, which is specialised in direct and proactive patient management in studies. This independence is important with respect to confidentiality concerns and safekeeping of the collected data.

At registry initiation, patients will be asked to sign a Contact Order Form (COF), which provides the patients' contact information and gives the permission to ProClinica™ to contact them for the registry. The COF will be sent to ProClinica™.

Induction biases will be controlled by training the interviewers who are requested to respect the call script and to be neutral during the assessment (no comment or reaction according to the responses given).

Regular quality controls of interviewers will be performed with regards to technical and communication skills, compliance with protocol and quality plan and good reporting.

Telephone calls performed by ProClinica™ are not a substitute for the HCP's relationship with his/her patient and patient follow up. If a medical question or problem arises during the phone call, the patient will be advised to contact his/her HCP.

ProClinica™ will never transfer any patients' contact details to the registry Sponsor, the monitor, the data-managers, or any other third party. Patients' health data are collected in an anonymous way, the patients are identified by the registry identification code (patient number, site number), and the patients' contact details are never linked to the patients' health data.

5.5 Site monitoring

REGISTRAT-MAPI has assumed one on-site monitoring visit per site for 80% of sites. Sites to be monitored can either be randomly selected or identified according to triggers. These triggers may include, but are not limited to, the following:

- Informed Consent Form (ICF) issues.
- Data integrity verification issues (documented or suspected).
- Concerns regarding appropriately qualified existing and/or new staff.
- Documented or observed data quality issues.
- Duplicated data results across patient contacts or across patients.
- Motivation.
- Unresolved issues that are not addressed in a timely manner.

The aims of these visits are to enable adequate communication with HCPs should potential issues be raised.

In addition, Clinical Research Associates (CRAs) will perform data quality checking (focusing on ECG recordings) in 10% of sites. REGISTRAT-MAPI assumes that HCPs will read the ECG recordings and complete the result in the CRF. The aim of these data quality control visits is to check key data of the CRF (i.e. ECG recordings) against the source data on a defined percentage of patients (i.e. 10%).

Communication with the sites via telephone will also enable REGISTRAT-MAPI to maintain contact with the site, to follow patient recruitment and the return of registry documents, and to address any issues that the site may have or any questions related to the registry. It is assumed that sites will be contacted via telephone 3 times per year. These telephone calls will enable REGISTRAT-MAPI to update the HCP with information about the registry, discuss any potential issues and, most importantly, to motivate them. These contacts are not burdensome for the HCP, but enable REGISTRAT-MAPI to keep contact with all investigators throughout the registry. A report will be written for each of the telephone calls and the content of the call can be adapted to the phase of the registry/updates on the registry.

6. BIAS AND LIMITS OF THE REGISTRY

Generally, three types of bias are distinguished in epidemiology and should be considered; selection, information and confounding bias. Potential biases and limitations of this 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 registry are related to the selection of the participating HCPs on one hand and to the selection of patients on the other hand.

HCP's representativeness:

The participating HCPs consist of a population of volunteers: this constitutes a classical non response selection bias for this type of registry.

To describe this potential bias, we propose to fill in a HCP recruitment registry form in order to collect certain information (e.g. speciality, geographic region, institution type) for all HCPs contacted and for all of the HCPs that initiate a contact themselves, whether or not they participate in the registry. 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 investigators 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 minimum data (e.g. patient age, gender, ethnicity) in the patient log for the Eurartesim™ registry, in order to allow comparison of the characteristics of included and non-included patients.

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.

Information bias could occur in this registry regarding the collection of lifestyle data, such as smoking status and alcohol consumption. Patients may under-report their smoking and alcohol consumption, which is an inherent limitation associated with the collection of lifestyle data.

Information bias could also occur in this registry 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, a data audit will be conducted on a 10% sample of HCPs randomly selected and/or selected by REGISTRAT-MAPI after review of completed and uploaded CRFs, to determine how well their medical records data matches the information provided in the Safety Registry for Eurartesim™.

6.3 Confounding bias

Confounding bias in a drug safety registry results from selective prescribing of a medication to more severe patients.

As a result of a higher background risk, the reported event rate may be higher and give the appearance of an elevated risk related to the use of the primary medication. The collection of the baseline information will help to identify the presence of elevated background risk so that event rates can be compared through sub-group analysis (those with or without prior event) to determine if the elevated risk is likely to be related to background risk or use of Eurartesim™.

6.4 Lost to follow-up

The follow-up duration for this safety registry will be approximately one month; thus, loss to follow-up in this registry should be minimal. However, the option for each patient to be contacted by ProClinica™ to be reminded of the study and followed-up has also been built into the registry, thereby further minimising any losses to follow-up.

Losses to follow-up can be related to the occurrence of a SAE; the direct and proactive approach of ProClinica™ to contact the patient, then a relative or the usual referral HCP, will minimise patient losses to follow-up for safety reasons.

According to routine clinical practice, most patients receiving Eurartesim™ for the treatment of malaria will be hospitalised for at least three days and follow-up will be conducted at hospital discharge. For the minority of patients who refuse hospitalisation, follow-up will be performed on an out-patient basis and the patients will be asked to contact their HCP with their test results (e.g. ECG recordings, blood withdrawal results), in order for the data to be recorded on the CRF. A follow-up visit is also recommended between three to five weeks after hospital (or out-patient treatment) discharge.

Patients will remain in the registry even if a follow-up visit is not performed. Patients will be flagged for telephone follow-up by ProClinica™ if their corresponding CRF has not been received after 15 days (for the discharge follow-up) and/or 45 days (for the three to five weeks after discharge follow-up).

During these follow-up telephone calls, ProClinia™ will collect data regarding:

- Concomitant medication use since last follow-up, including any other treatment taken for malaria (including prescription dates).
- Any AEs/SAEs/AESIs since last follow-up.
- Patient status.

Patients will be considered lost to follow-up if patient follow-up information has not been entered into the registry within 3 months of the date of Eurartesim™ initiation. Reasons for loss to follow-up (e.g. patient not contactable) will be documented.

If patients are lost to follow-up, any data collected up to that point (including any adverse event data, e.g. QTc prolongation) will be included in the statistical analyses (including analysis of the adverse event outcome, e.g. QTc prolongation).

7. SAFETY MANAGEMENT

7.1 Definitions

An **Adverse Event (AE)** is defined as any untoward medical occurrence in a patient administered a medical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (for example, 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 this medicinal product.

An **Adverse Drug Reaction (ADR)** concerns noxious and unintended responses to a medicinal product. A reaction, in contrast to an event, is characterized by the fact that a causal relationship between the medical product and the adverse event is at least a reasonable possibility.

For regulatory reporting purposes on post approval safety data, if an AE is spontaneously reported, even if the relationship is unknown or unstated, it meets the definition of an ADR.

Serious AE/ADR (SAE/SADR):

Preamble: "Serious" and "Severe" are not synonymous. The term "severe" is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a severe headache). This is not the same as "serious", which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

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

- Results in **death** of the patient.
- Is **life-threatening:** this refers to an event/reaction in which the patient was at risk of death at the time of the event/reaction; it does not refer to an event/reaction which hypothetically might have caused death if it were more severe.
- Requires **in-patient hospitalisation:** an event/reaction 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.
- Results in **prolongation of existing hospitalisation:** an event/reaction that occurs while the study patient is hospitalised and prolongs the patient's hospital stay.
- Is a **congenital anomaly/birth defect:** an anomaly detected at or after birth, or any anomaly that results in fetal loss.
- Results in **persistent or significant disability/incapacity:** an event/reaction 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).
- **Is a medically important event or reaction:** an important medical event/reaction that may not be immediately life-threatening or result in death

or hospitalisation, 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/birth defect, 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 hospitalisation, or the development of drug dependency or drug abuse.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious ADR.

Severity assessment

The HCP will use the following definitions to rate the severity (not seriousness) for any adverse event being collected as an endpoint/datapoint in the registry 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.

Relatedness assessment

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

- **Related:** An adverse event has a strong temporal relationship to study drug or recurs on re-challenge and another etiology is unlikely or significantly less likely or a more likely alternative etiology exists.
- **Not related:** An adverse event is due to an underlying or concurrent illness or effect of another drug and is not related to the study drug (e.g., has no temporal relationship to study drug or has a much more likely alternative etiology), or an adverse event has little or no temporal relationship to the study drug and/or a more likely alternative etiology exists.
- **Unassessable:** a reasonable judgment cannot be made (e.g., key information is missing)

Except for an adverse event which has a strong temporal relationship to study drug alternate etiology must be provided by the HCP for the adverse event.

Spontaneous reports: unsolicited communication by a healthcare professional or consumer to a company, regulatory authority or other organization that describes one or more ADRs in a patient who was given one or more medicinal products and that does not derive from a study or any organized data collection scheme.

Solicited reports are those derived from organized data collection systems, which includes clinical trial, registries, post-approval named patient use programs, other patient support and disease management programs, survey of patients or healthcare providers or information gathering on efficacy or patient compliance.

7.2 Non-Serious AE/ADR reporting

All AEs (potentially related or not-related to Eurartesim™) will be recorded in the CRF.

7.3 Serious Adverse Event reporting

Reporting of safety events related to Eurartesim™ to regulatory authorities will be performed by Sigma-Tau. REGISTRAT-MAPI will be responsible for ensuring that any suspected SAE is followed-up by the HCP and that all available necessary declarative information is obtained within 72 hours from the HCP and made available to the pharmacovigilance department of Sigma-Tau. REGISTRAT-MAPI will work in close collaboration with Sigma-Tau's pharmacovigilance department and will ensure that HCPs transmit the necessary safety information for Sigma-Tau to report the event as necessary to comply with expedited reporting requirements.

By Registry HCP

In the event of a **serious** AE/ADR (as defined in Section 7.1) in a patient treated with Eurartesim™, 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.

It will be the HCP's responsibility to report any serious adverse events related to products other than Eurartesim™ to the respective marketing authorization holder and/or to the regulatory authorities as per local regulatory requirements.

By ProClinica™ and REGISTRAT-MAPI:

In addition to solicited reporting of adverse events, as described in this protocol, spontaneous reporting of a potential serious adverse drug reaction to Eurartesim™ 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 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 registry-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.

7.4 Adverse Event of Special Interest reporting

The following AESIs are to be recorded and reported in the same way as SAE/SADR:

- Torsade de Pointes (TdP).
- Sudden death.
- Ventricular tachycardia.
- Ventricular fibrillation and flutter.
- Syncope.
- Seizures.
- Sustained arrhythmias (repetitive or lasting >30 sec at a ventricular rate >120 bpm).

7.5 Pregnancy reporting

Any pregnancy where the foetus may have been exposed to Eurartesim™ through maternal exposure should be notified by the HCP.

Outcome of the pregnancy (normal or abnormal) should be recorded.

Abnormal pregnancy outcome in association with Eurartesim™ should be notified on an expedited basis (i.e. within 24 hours of the HCP becoming aware of the abnormal pregnancy outcome; refer to Section 7.3). This refers especially to congenital anomalies in the foetus/child, foetal death and spontaneous abortion, and adverse reactions in the neonate that are classified as serious.

Pregnancy will be recorded as an AE in all cases. It will be qualified as a SAE only if it fulfills SAE criteria.

The HCP should also refer the pregnant woman for enrolment in the 'Pregnancy Registry for Eurartesim™' registry. The HCP will be aware of the pregnancy registry, as the sites included in this safety registry are sampled from those included in the pregnancy registry.

7.6 Sigma-Tau pharmacovigilance database

Sigma-Tau will set-up and maintain a pharmacovigilance database for Eurartesim™. Some key data extracted from the SAE Report Forms will also be entered by REGISTRAT-MAPI into the 'Safety Registry for Eurartesim™' registry, in order to enable statistical analysis of the safety profile of Eurartesim™ and to provide listings of the SAEs recorded during the registry.

8. REGISTRY TIMELINES

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

Validation of study documents:	June2012
Ethics submission:	June 2012
Launch of Eurartesim™:	June 2012
First patient in:	July 2012
Last patient in:	April 2015
Database lock:	July 2015
Final Clinical Study Report:	October 2015

9. ETHICS CONSIDERATIONS

9.1 Ethical conduct of the registry

The registry 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 registry 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 registry will be obtained from medical notes and information provided by the patients.

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

9.1.1 Ethics Committee (EC)

Ethical submissions will be performed as required by local legislation in each country involved in the registry. The necessary ethical approvals will be obtained for each site before initiation of the site. The registry is observational. Choice by the HCP of the drug used to treat the patient is based on clinical judgment 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 registry purposes.

9.1.2 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.

9.1.3 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.

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 a follow-up of patients, with collection of longitudinal information
- 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 registry, 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 agreement – of their right to access, object to and correct this information.

For France, since the personal data collected in this registry are processed in France before transfer to the Sponsor, this registry is governed by chapter IX of the amended French Data Processing and Privacy Law of 6 January 1978. It must be of a request for approval from the Advisory Committee on Information Processing in Material Research in the Field of Health (CCTIRS) and a request for authorization from the French National Commission for Data Processing and Privacy (CNIL).

Ethical and personal data protection considerations regarding contacts with patients (ProClinica™):

Patients or their legal representative will be asked to complete and sign a 'Contact Order Form' (COF). This "Contact Order Form" will be 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 ProClinica™ to perform the contacts as described in the protocol during the registry follow-up period.

Additionally, by signing this form it is documented that patients have been 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 will be tacitly renewed with each assessment.

The ProClinica™ unit will never transfer any patients' contact details to the registry Sponsor, the monitor, the data-managers, or any other third party not directly involved in its mission. Patients' health data will be collected in a de-identified way, using a registry identification code (e.g. patient number, site number). The patients' contact details will never be linked to the patients' health data and the patients' contact details, including COFs, will be erased at the end of the registry from all data support systems (computer and paper).

All interviewers working on the registry will sign a professional secrecy agreement, will be trained specifically to the registry and to data privacy rules, as well as supervised and quality controlled throughout the registry. The Medical Direction of ProClinica™ unit will intervene when necessary. Patient return calls by a HCP will be performed when needed, i.e. depending on the content of the discussion with the patient, the HCP may be asked to call the patient back (e.g. if a problem is suspected).

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 will never interfere with the usual relationship between patients and healthcare professionals. On the contrary, they will promote it. They will be required not to comment on any prescription or give any advice or response to medical/registry 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) will be 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 1). 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*).

9.1.4 Information and patient consent

The HCP will give the patient a patient information and Informed Consent Form (ICF) at the inclusion visit. This ICF will contain information concerning the nature and purpose of the registry, 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 amended "Data processing and privacy" law of 6 January 1978).

Before any procedure associated with the registry is carried out, the patient information and consent 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.

9.2 Audit

The Sponsor will be able to conduct audits in order to verify that collected data are reliable and that the registry is conducted according to the protocol and to the applicable regulatory requirements.

10. FINAL REPORT AND PUBLICATIONS

At the end of the registry, REGISTRAT-MAPI EU will provide a final study report that will be reviewed by Sigma-Tau and the CAB. This report will contain a description of the objectives of the registry, the methodology, the results and the conclusions of the registry. 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.

An interim report will be generated annually (cumulative data), which will include a section for monitoring patient enrolment rates. Interim reports may not be released to unauthorized people in any form (publications or presentations) without express written approval from Sigma-Tau.

Both the interim and final reports will be generated by REGISTRAT-MAPI EU, in accordance with a detailed statistical analysis plan approved by Sigma-Tau, the CAB and the EMA. The final report will be rendered available within six months from registry closure.

Tables and listings (generated with SAS software) will be produced to enable reporting of key interim outcomes to:

- Regulatory authorities.
- CAB.

The final study results will be reported to:

- Regulatory authorities.
- CAB.
- All participating HCPs.

Summary of the registry results will be distributed to the medical community at large.

Reporting of data will be in aggregate form to ensure individual patient and HCP confidentiality.

11. RETENTION OF REGISTRY DOCUMENTATION

Sigma-Tau will maintain the data collected (questionnaires and databases) for 5 years (or a longer retention period if specified and authorised) after the registry has been completed.

12. COORDINATION

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

Dr Maurizio Iannuccelli

Head of Corporate Human Safety

Sigma-Tau

Regulatory Development & Corporate Safety

Email: maurizio.iannuccelli@sigma-tau.it

Tel: +39 06 9139 3925

and

Dr Antonella Bacchieri

Head of Biostatistics and Data Management

Sigma-Tau

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

Charlotte Brown

Senior Project Manager

REGISTRAT-MAPI

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14. APPENDICES

APPENDIX 1: PROCLINICA™ CNIL ACKNOWLEDGEMENT OF RECEIPT

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".

Sylvie ODEZENNE
Traducteur Expert
près la cour d'Appel de Grenoble
ATI - TRANSWORD - 10, place Charles Béraudier
69003 LYON - 04 26 68 70 50

Paris (France), 15 March 2011

Alex Türk

By delegation of the Authority
Alex Turk

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FRENCH REPUBLIC

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