Epidemiological Study Report

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Product reference	EU/1/11/716/001-005
Procedure number	***EMEA/H/C/001199***
Marketing authorisation holder	ALFASIGMA Via Ragazzi del '99, 5 - 40133 Bologna - Italy
Joint PASS	No
Research question and objectives	The primary objective of this study is to assess the live birth incidence of minor and major congenital birth defects following exposure to Eurartesim® whilst pregnant or in the one (1) month (30 days) prior to conception. The secondary objective of this study was to assess both maternal and fetal outcome following exposure to Eurartesim® whilst pregnant or in the one (1) month (30 days) prior to conception.
Countries of study	Nine European countries: Belgium, France, Germany, Ireland, Italy, the Netherlands, Portugal, Spain and the UK.

Author	Yann BOURHIS Medical Writer ICON 27 rue de la Villette | 69003 Lyon | France Tel: +33 (0) 472355305 Email: Yann.Bourhis@iconplc.com

Marketing authorisation holder

Marketing authorisation holder	ALFASIGMA Via Ragazzi del '99, 5 40133 Bologna, Italy
MAH contact person	Giovanni Mattera, MD Clinical Safety Unit, Manager Corporate R&D Tel: +39 0691393382 | mobile: +39 3881444145 Email: giovanni.mattera@alfasigma.com

Contract Research Organisation

Contract Research Organisation	ICON
CRO contact person	Isabelle Grand Project Manager 27 rue de la Villette | 69003 Lyon | France Tel: +33 (0) 426556986 Email: Isabelle.Grand@iconplc.com

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PREGNANCY REGISTRY FOR EURARTESIM®

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AUTHOR:

Yann Bourhis
Medical Writer

Signature: Date: 18APR2019

REVIEWS AND APPROVALS:

For the Sponsor

Giovanni Mattera, MD
Responsible for Medical Review

Signature: Date: 18.04.201

Nadia Canova
Head of Corporate
Pharmacovigilance - EUQPPV

Signature: Date: 18.04.20

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1 SYNOPSIS

1.1 Title

PREGNANCY REGISTRY FOR EURARTESIM®

1.2 Keywords

Malaria, artenimol, piperaquine, pregnancy, safety

1.3 Rationale and Background

Eurartesim® is an artemisinin-based combination therapy (ACT), which involves the simultaneous use of two blood schizontocidal medicines with independent modes of action: artenimol [Dihydroartemisinin - DHA] and piperaquine tetraphosphate [PQP].

European marketing authorization for Eurartesim® was obtained on 27 October 2011 for the treatment of uncomplicated Plasmodium falciparum malaria.

The Summary of Product Characteristics (SmPC) states that Eurartesim® should not be used during pregnancy in situations where other suitable and effective antimalarials are available.

The European Medicines Agency (EMA) requested that ALFASIGMA conducted a study in order to ensure that data regarding Eurartesim® use for the treatment of malaria whilst pregnant are collected, in particular on populations with limited data (e.g., Caucasians).

This report presents the information collected in the pregnancy registry for Eurartesim®.

1.4 Research Question and Objectives

Primary objective:

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

Secondary objectives:

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

1.5 Study Design

This was an observational, non-comparative, non-interventional, longitudinal, multi-centre registry for female patients exposed to Eurartesim® for the treatment of malaria whilst pregnant, conducted in 9 European countries: Belgium, France, Germany, Ireland, Italy, the Netherlands, Portugal, Spain and the UK.

Health care professionals (HCPs) were to include all patients meeting the inclusion criteria and agreeing to take part in the registry. Diagnosis of malaria was to be clinically and parasitologically confirmed.

As an observational study, this registry did not change the patient-HCP relationship, nor influence the HCPs' drug prescription or therapeutic management of the patient.

1.6 Settings

HCPs known to treat and follow-up malaria patients were invited to collaborate in this registry.

An invitation letter including a summary of the study and a reply form were sent out to the HCPs in each country. HCPs were asked to provide their response as well as information about the site (e.g., speciality, type of institution/practice, number of patients seen, reasons for refusal) using the reply form Site information. Non-respondent HCPs were contacted by telephone.

In addition, women who were not followed in one of the selected sites had the possibility to contact their HCP and ask them to contact Alfasigma on their behalf in order to be included in the registry. Furthermore, all patients with pregnancies reported to the company as spontaneous events by HCPs were also to be asked to participate in the pregnancy registry. All spontaneous events (e.g., pregnancy exposure, birth defects) were to be reported, regardless of the country.

Moreover, an educational 'outreach program' was implemented to increase awareness of the registry among both patients and HCPs, and increase both patient and HCP participation:

- Patient Information Sheet included with product packaging (including contact data for each country);
- Targeted educational material to inform HCPs of the registry and provide information on how to refer patients for inclusion and participation;
- Registry website to provide patients and HCPs with information regarding the registry, and to describe the process for participation for both patients and HCPs, including relevant contact details;
- Web awareness activities, including advertisements and links on relevant sites, and internet based recruitment;
- Advertising and scientific presentations at specifically targeted meetings such as the European Society of Clinical Microbiology and Infectious Diseases;
- Partnering with interested organisations: European Network of Teratogen Information Services (ENTIS), European Surveillance Network of Congenital Anomalies (EUROCAT), European Collaboration of Craniofacial Anomalies (EUROCRAN), International Clearinghouse for Birth Defects Monitoring Systems.

A review of literature was performed routinely to ensure that HCPs publishing any relevant maternal exposure were contacted for inclusion in the registry.

Participating HCPs were asked to include all patients meeting the inclusion criteria and agreeing to take part in the registry. During the recruitment phase, and for each patient, the HCP had to:

- Explain the registry (in particular the objective of the registry and its observational nature).
- Give her a patient information sheet, a consent form and ask her to read and sign it to confirm her agreement to participate in the registry.

- Ask her to complete and sign a contact order form (COF) to allow ProClinica™ to contact her during the study follow-up. The patient was asked to provide her contact details, the contact details of a relative and the contact details of her treating physician, obstetrician/gynaecologist, and paediatrician, and to authorize ProClinica™ to contact them, as applicable. The COF was to be sent by fax or email to ProClinica™.
- Complete the enrolment CRF of the registry.

After enrolment, patient data were to be collected at the following timepoints:

- 4 weeks post-enrolment;
- 4 weeks pre-delivery;
- at delivery;
- 6 weeks post-delivery.

In addition, infant data were to be collected 6 weeks, 14 weeks and 12 months after birth.

At each follow-up visit/contact, the HCP was to complete the corresponding follow-up CRF of the registry.

Safety assessments included monitoring and recording of all AEs and SAEs up to 12 months after delivery. For a given adverse outcome, additional information regarding relevant medical history and family history could be collected.

In addition to data collected by HCPs during visits and in order to minimize lost-to-follow up rates, a supplementary system of active patient follow-up was undertaken by ProClinica™, which is specialised in direct and proactive patient management in studies. ProClinica™ intervention was triggered by the non-reception of the CRF in due time as follows:

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

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

The main objective of these contacts was to remind the patient of the importance to comply with the registry assessment schedule, to detect and document the reasons for non-collection of information (i.e., serious safety event, withdrawal from the study, personal reason). A structured short screening of pregnancy outcome, easy to understand by patients, was to be performed and documented. A copy of the completed screening questionnaire was to be systematically sent to the concerned registry HCP. In the event of an abnormal pregnancy outcome and/or a serious safety event on the child, the concerned registry HCP was to be asked to follow up and medically confirm the event. If the concerned registry HCP was not able to manage this medical confirmation, ProClinica™ was to seek to get a medical confirmation through patient treating HCPs.

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

Patients were considered lost to follow-up if the expected delivery date was passed, if no outcome data were collected within one year of the expected delivery date, and if all contact attempts failed. Reasons of loss to follow-up (e.g., patient not contactable, moved away, died) were to be documented.

1.7 Subjects and Study Size

Selection criteria

Inclusion Criteria:

The following patients were to be included in the registry:

Women;

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

Exclusion Criteria:

The following patients could not be included in the registry:

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

Number of Patients (Expected)

A sample size of 376 pregnant women exposed to Eurartesim® were to be enrolled in order to detect a significant difference (i.e., ≥ 2-fold increase in the outcome of concern) relative to the expected background rate of all birth defects and spontaneous abortions.

1.8 Variables and Data Sources

1.8.1 HCP enrolment form

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

1.8.2 Case Report Form

Patient data

At enrolment visit:

- Date of the visit;
- Socio-demographic characteristics of the mother (ethnicity [based on the standard definitions of ethnicity used in the EU country where the woman is enrolled in the Registry], country of birth, primary language and socio-economic status [based on current or most recent occupation and years of formal education]);
- Socio-demographic characteristics of the biological father (age and current or most recent occupation);
- Mother's lifestyle data (height [cm] and weight [kg], radiation exposure, smoking status [never/past/current], alcohol consumption [weekly units], recreational drug use;
- Mother's malaria history (date of malaria diagnosis, date of most recent Eurartesim® administration and dose, previous Eurartesim® administrations, other treatment taken for malaria);
- Pregnancy data (date the pregnancy was registered);
- Estimated date of delivery/date of last menstrual period;
- Previous or concurrent maternal complications;
- Health status of the fetus, if it is already known at time of enrolment, i.e. via ultrasound;
- Pregnancy outcome, if already known at time of enrolment;
- Obstetrical history (number of previous pregnancies and outcome);
- Significant medical history of the mother and the biological father;
- Concomitant medication use in the mother and the biological father in the one (1) month (30 days) prior to conception.

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

- Date of the visit;
- Adverse events (AEs), adverse events of special interest (AESIs) and serious adverse events (SAEs), drug related or not, in the mother since previous visit/contact;

  The following AEs were defined as AESIs:

  - Cardiotoxicity: prolonged QT/QTc, fainting/syncope, palpitations, pounding/pain in the chest area, convulsion, torsade de pointes (TdP), ventricular fibrillation/Flutter, ventricular tachycardia, sustained arrhythmias (repetitive or lasting >30 sec at a ventricular rate >120 bpm)
  - Neurotoxicity: abnormal behaviour, convulsion, dizziness, febrile convulsion, hallucination, stroke, paraesthesia, tinnitus
  - Phototoxicity: dermatitis, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular
- Exacerbation of pre-existent clinical condition in the mother since previous visit/contact;

- Comorbidities in the mother since previous visit/contact;
- Concomitant medication use in the mother since previous visit/contact;
- Maternal complications since previous visit/contact;
- Fetal complications since previous visit/contact; any spontaneous abortions (≤28 weeks gestation), elective abortions, ectopic pregnancies, late fetal or neonatal deaths (>20 weeks gestation), premature deliveries (≤37 completed weeks).

At end of pregnancy:

- Date of the end of pregnancy;
- Maternal complications since previous visit/contact;
- Maternal mortality;
- Stillbirth (>28 weeks gestation);
- Early neonatal mortality;
- Gestational age at delivery (estimated from the last menstrual period);
- Live births;
- Infant birth weight (adjusted for gestational age);
- Infant major and minor birth defects (primary outcome of interest);
- Adverse events (AEs, AESIs and SAEs), drug related or not, in the mother or the infant since previous visit/contact;
- Exacerbation of pre-existent clinical condition in the mother since previous visit/contact;
- Comorbidities in the mother since previous visit/contact;
- Concomitant medication use in the mother since previous visit/contact.

6 weeks after end of pregnancy:

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

14 weeks after end of pregnancy:

- Date of the visit;
- Maternal complications since previous visit/contact;
- Maternal mortality;
- Infant mortality;

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

12 months after end of pregnancy:

- Date of the visit;
- Adverse events (AEs, AESIs and SAEs), drug related or not, in the mother or the infant since previous visit/contact.

Infant development / assessment of pregnancy outcomes

At birth:

- At birth, ProClinica™ was to contact the patient's obstetrician/gynaecologist and general practitioner to obtain medical confirmation of events, e.g., premature delivery, stillbirth, birth defects.

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

- After birth, ProClinica™ was to contact the infant's paediatrician to obtain medical confirmation of events, e.g. birth defects, infant development, neonatal death;
- "Birth defect" was defined as a major congenital abnormality or syndrome with exclusion for related minor abnormalities, as defined by EUROCAT (EUROCAT, 2009). HCPs were to record any infant birth defect(s) on the CRF in free text. This was then to be coded in-house using both MedDRA and ICD-10 codes (ICD-10 Chapter XVII: congenital malformations, deformations and chromosomal abnormalities, as recommended by EUROCAT) to enable comparisons and transfer of data between other sources.

1.9 Statistical Methodology

Given the limited number of patients included in the registry, patient data were only presented in listings (See Appendix 2.2).

1.10 Results

In total, 50 HCPs were contacted and 36 agreed to participate in the registry and had an initiation visit.

Overall, 2 women were enrolled in the pregnancy registry.

- Patient 320001-1 (included in Belgium):

The Patient 320001-1 was a 25-year old Black woman from Ghana (primary language: Flemish). At inclusion, the patient was 107 kg. She never smoked, never drank alcohol or only on special occasions (less than once a week), and took no recreational drugs. She worked as a service worker / shops and market sales worker. She had never been exposed to radiations.

The pregnancy was registered on 12 June 2015. This was patient's first pregnancy. She took some medications within the month prior to conception. No information about the biological father was recorded.

Malaria was diagnosed on 30 July 2015. Eurartesim® treatment started on 3 august 2015 for 3 days (daily dose: 4 tablets of Eurartesim® 320/40 mg). The patient was also treated with Riamet (for malaria) and Ciproxine (for fever) from 01 to 03 July 2015, with Dalacin (for malaria) from 31 July to 06 August 2015 and with Losferon (for anemia) from 06 august 2015 (still on-going on 02 September 2015, no further information provided afterwards).

The patient was followed in the registry up to 25 October 2016. No adverse events, exacerbation of any pre-existent clinical condition, comorbidities, and maternal nor fetal complications were reported. The patient gave birth to a healthy girl on 13 October 2015 at a gestational age of 40 weeks (weight: 2800 g, height: 50 cm). The APGAR score 1' was 9 and the APGAR score 5' was 10. Three months after infant's birth, the infant was developing well.

- Patient 390015-1 (included in Italy):

Patient 390015-1 was a 29-year old Black woman from Nigeria (primary language: English). At inclusion, she was 65 kg and 166 cm. She had 10 years of formal education and worked as craft and related trades worker. The patient never smoked, never drank alcohol or on special occasions (less than one week), and took no recreational drugs. She had never been exposed to radiations.

The pregnancy was registered on 23 February 2015. This was not patient's first pregnancy. She took no medications within the month prior to conception. The biological father was 39 years old and worked as a clerk. He took no medications within the month prior to conception.

Malaria was diagnosed on 8 October 2015. Eurartesim® treatment started on 8 October 2015 for 3 days (daily dose: 3 tablets of Eurartesim® 320/40 mg). No concomitant medications were reported.

The patient was followed up to 14 November 2015. No adverse events, exacerbation of any pre-existent clinical condition, comorbidities, and maternal nor fetal complications were reported. The patient gave birth to a healthy boy on 14 November 2015 at a gestational age of 37.5 weeks (weight: 2300 g). The APGAR score 1' was 9 and the APGAR score 5' was 10.

A ProClinica™ contact was done 3 months after the expected delivery. The mother and the baby did not experience any serious health problems since the last contact with the investigator.

1.11 Discussion - Conclusion

Patient recruitment in the registry was very limited, notwithstanding considerable sustained efforts made by the MAH to raise awareness of the registry among both patients and HCPs via the educational 'outreach program' and to keep the sites opened from 2012 to 2018. This is however consistent with the findings of the feasibility study conducted in November/December 2010. In fact, pregnant women infected with malaria are very rare in Europe and furthermore, very few of them are Caucasian.

No safety signals were detected in the 2 patients included in the registry.

1.12 Marketing Authorisation Holder

ALFASIGMA
Via Ragazzi del '99, 5
40133 Bologna, Italy