Pharmaco-epidemiological study protocol

Protocol N° 3366

1. STUDY TITLE

Effectiveness evaluation survey for Eurartesim™

Version:	Final
Amendment:	NA
Date :	15 July 2013

2. MARKETING AUTHORIZATION HOLDER

Sigma-Tau
Via Pontina km 30,400
00040 Pomezia (Rome)
ITALY

3. RESPONSIBLE PARTIES

Sponsor Representative

Dr Maurizio Iannuccelli

Drug Safety Physician

Biostatistics and Pharmacovigilance

Sigma-Tau

Email: maurizio.iannuccelli@sigma-tau.it

Tel: +39 06 9139 3925

Dr Antonella Bacchieri

Head of Biostatistics and Pharmacovigilance

Sigma-Tau

Email: antonella.bacchieri@sigma-tau.it

Tel: +39 06 9139 3543

Mapi Representative

Charlotte Brown

73 Collier Street, London N1 9BE, UK

Tel/Fax.: +44 (0) 800 098 8601

APPROVAL

Effectiveness evaluation survey for Eurartesim™

Final version date: 15 JUL 2013

Protocol N° 3366

Final version

For the Sponsor		
Dr Maurizio Iannuccelli Head of Pharmacovigilance Medical Functions	Signature:	Date: 19 JAN 2015
Dr Antonella Bacchieri Head of Biostatistics and Pharmacovigilance	Signature:	Date: 19-01-2015
Dr Houghton Leona EU-QPPV	Signature:	Date: 19/1/2015
For Mapi		
Charlotte Brown Project Manager	Signature:	Date: 19JAN2015
Stéphanie Chrétin Statistician	Signature:	Date: 19JAN2015
Yann Bourhis Medical Writer	Signature:	Date: 19 JAN 2015

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LIST OF ABBREVIATIONS

ACT	Artemisinin-based Combination Therapy
AE	Adverse Events
CAB	Clinical Advisory Board
DHA	Dihydroartemisinin
EC	Ethics Committee
EMA	European Medicines Agency
GP	General Practitioner
HCP	Healthcare Provider
KOL	Key Opinion Leader
MedDRA	Medical Dictionary for Regulatory Activities
MMV	Medicines for Malaria Venture
PQP	Piperaquine
SAE	Serious Adverse Events
SMA	Site Monitoring Associate

4. ABSTRACT

4.1 Title

Effectiveness evaluation survey for Eurartesim™

4.2 Rationale and Background

The European Medicines Agency (EMA) has requested Sigma-Tau to provide all physicians who are expected to prescribe or use Eurartesim™ with a healthcare professional educational pack. The EMA has requested Sigma-Tau to perform an Effectiveness survey in order to further assess physician understanding of this education material.

This protocol details strategy consideration for an Effectiveness survey in 3 European countries for physicians who are expected to prescribe or use Eurartesim™ for the treatment of malaria.

4.3 Research Question and Objectives

Primary Objective

- To ascertain the physician understanding of the education material provided about Eurartesim™, in terms of drug indication, prescription modalities, administration modalities, high-risk patients, and potential side effects.

Secondary Objectives

- To ascertain physician awareness of the pregnancy and safety registries.
- To ascertain physician awareness of available information sources regarding the medication.

4.4 Study Design

Observational, European multi-centre survey, conducted in France, Spain and the United Kingdom (UK).

The survey will be conducted respectively 12 months and 24 months after Eurartesim™ education material is delivered to the Physicians by the Sponsor.

Physicians will be selected among a list of approximately 300 physicians per country, provided by the Sponsor.

Approximately 60 Physicians per country are expected to participate.

The following selection process will be conducted in each country respectively 12 months and 24 months after Physicians received education material:

- A recruitment mail containing the study summary and a participation form will be sent to all Physicians.
- Physicians will be asked to send back the completed participation form to Mapi. Characteristics of physicians, and if applicable, reason for non participation will be collected on the participation form.
- Non-respondent Physicians will be contacted by telephone by Site Monitor Associates (SMAs), to know if they agree or not to participate in the survey.
- The survey questionnaire will be administered by the SMAs by phone to the Physicians selected for the survey and willing to participate.

4.5 Population

Selection criteria:

- Physicians known to treat and follow-up patients with malaria
- Physicians not participating in Pregnancy and Safety registries
- Physicians who agree to participate in the survey

4.6 Variables

The following data will be collected:

Physician characteristics:

- Specialty
- Geographic location
- Institution type
- Years in practice
- Number of malaria patients currently treated
- Experience with Eurartesim™ (Number of patients treated the previous year, number of months since last patient treated with Eurartesim™)

Survey questionnaire:

- Date of questionnaire completion
- Knowledge of the drug
- Reception of education material on Eurartesim™
- Indication of Eurartesim™
- Prescription modalities
- Administration modalities
- Effects on cardiac repolarization
- High-risk patients
- Potential side effects
- Awareness of the pregnancy and safety registries
- Information sources on Eurartesim™

4.7 Data Sources

Data will be collected through a survey questionnaire administered by phone by SMAs to Physicians willing to participate.

4.8 Study Size

Assuming that 20% of Physicians agree to participate in the survey, approximately 60 participating Physicians per country are expected.

4.9 Data Analysis

The statistical analysis will be carried out using SAS software version 9.2.

It will be conducted for 12-month and 24-month surveys, separately, on data collected from all participating Physicians and for each country.

A Statistical Analysis Plan will be prepared by Mapi and approved by the Sponsor before the data-base is frozen.

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 and the number of missing data. 95% confidence intervals will be computed on each individual percentage.

Description of the study population:

Characteristics of participating Physicians will be described.

Response to the primary objective:

- Knowledge of indication of Eurartesim™ will be described
- Knowledge of prescription modalities of Eurartesim™ will be described
- Knowledge of administration modalities of Eurartesim™ will be described
- Knowledge of effects on cardiac repolarization will be described
- Knowledge of high-risk patients will be described
- Knowledge of potential side effects of Eurartesim™ will be described

Response to the secondary objectives:

- Awareness of the pregnancy and safety registries will be described
- Awareness of available information sources regarding Eurartesim™ will be described

4.10 Milestones

Study Milestone	Estimated Date
Ethics submission	July 2013
12-month survey	September 2013 – March 2014
Statistical analyses	May 2014
Interim Study Report	June 2014
24-month survey	September 2014 – March 2015
Statistical analyses:	May 2015
Final Study Report	June 2015

5. AMENDMENTS AND UPDATES

This section is not applicable (original protocol).

6. MILESTONES

Study Milestone	Estimated Date
Ethics submission	July 2013
12-month survey	September 2013 – March 2014
Statistical analyses	May 2014
Interim Study Report	June 2014
24-month survey	September 2014 – March 2015
Statistical analyses:	May 2015
Final Study Report	June 2015

7. BACKGROUND AND RATIONALE

7.1 Background

Malaria is one of the most important public health problems in terms of morbidity and mortality, causing more than 200 million cases and 655.000 deaths every year [1].

According to the World Health Organization (WHO) Malaria Report 2011, a total of 106 countries in the world are at risk of transmission of malaria infection. A total of 216 million estimated malaria cases occurred in 2010, 81% of which were reported in the African Region, followed by South East Asia (13%) and Eastern Mediterranean Regions (5%) [1].

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. ACT is considered to be often more effective and to prevent or to delay the emergence of resistance [2].

Substantial data are available regarding potential side-effects of the active substances of Eurartesim™ (DHA and PQP) alone or in combination in patients [3]. In adults, the most common side-effects observed with Eurartesim™ (≥1/100 to < 1/10), are anaemia, headache, QTc (corrected QT segment length) prolongation, tachycardia, asthenia and pyrexia. In children, the most common side-effects observed with Eurartesim™ use ((≥ 1/10), are influenza, cough and pyrexia [4]. As a result of the findings from animal studies with dihydroartemisinin (DHA), Eurartesim™ should not be used during pregnancy if other suitable and effective antimalarials are available. In addition, women should not breastfeed during treatment with Eurartesim™.

In human subjects, small changes in the QTc have been reported after DHA/PQP administration, with no clinically significant cardiotoxicity [5,6]. Evaluation of the torsadogenic risk of DHA and PQP revealed that although there was such a risk, it was lower than for Chloroquine and Halofantrine and in the same range as for Mefloquine and Lumefantrine [7].

In addition, the potential QTc prolongation of Eurartesim™ is significantly reduced when Eurartesim™ is administered in fasting conditions with water [4]. Data indicate that co-administration of Eurartesim™ with fat increases the bio-availability of PQP, which may increase its effect on the QTc interval [8].

7.2 Study Rationale

The European Medicines Agency (EMA) has requested Sigma-Tau to provide all physicians who are expected to prescribe or use Eurartesim™ with a healthcare professional educational pack containing the following:

- The Summary of Product Characteristics
- The Patient Information Leaflet
- The Physician Leaflet including the Contraindicated Conditions of Use and Contraindicated Concomitant Medication checklist

The Physician Leaflet should contain the following key messages:

- Eurartesim™ has a potential to prolong the QTc interval that may lead to potentially lethal arrhythmias.
- Piperaquine absorption is increased in the presence of food, therefore to reduce this risk of QTc interval prolongation, the patients should be advised to take the tablets with water, without food, no less than three hours after the last food intake. No food should be taken within 3 hours after each dose.
- Eurartesim™ is contraindicated in patients with severe malaria according to WHO definition and in patients with a history of clinical conditions that may lead to QTc interval prolongation, and in patients taking drugs that are known to prolong the QTc interval.
- The ECG monitoring recommendations.
- The scope and use of the Contraindicated Conditions of Use and Contraindicated Concomitant Medication checklist.
- There is a potential risk of teratogenicity and so Eurartesim™ should not be used during pregnancy in situations where other suitable and effective anti-malarials are available.
- Need to counsel patients on important risks associated with Eurartesim™ therapy and appropriate precautions when using the medicine.
- Patients should be advised to contact their doctor about adverse events and physicians/pharmacists should report suspected adverse reactions to Eurartesim™, and in particular, those associated with a QT prolongation.
- The existence and scope of the pregnancy register and details of how to enter patients in it.
- In countries where the Safety registry is available, the educational material should include details on the registry and how to enter patients in it.

The EMA has requested Sigma-Tau to perform an Effectiveness survey in order to further assess physician understanding of the education material.

This protocol details strategy consideration for an Effectiveness survey in 3 European countries for physicians who are expected to prescribe or use Eurartesim™ for the treatment of malaria.

8. RESEARCH QUESTION AND OBJECTIVES

Primary objective:

To ascertain the physician understanding of the education material provided about Eurartesim™, in terms of drug indication, prescription modalities, administration modalities, high-risk patients, and potential side effects.

Secondary objectives:

- To ascertain physician awareness of the pregnancy and safety registries.
- To ascertain physician awareness of available information sources regarding the medication.

9. RESEARCH METHOD

9.1 Study Design

This is an observational, European multi-centre survey, conducted in France, Spain and the United Kingdom (UK).

The survey will be conducted respectively 12 months and 24 months after Eurartesim™ education material is delivered to the Physicians by the Sponsor.

9.2 Setting

9.2.1 Physician Selection

9.2.1.1 Selection Criteria

The following Physicians will be included in the study:

- Physicians known to treat and follow-up patients with malaria.
- Physicians not participating in Pregnancy and Safety registries.
- Physicians who agree to participate in the survey.

9.2.1.2 Sampling

Physicians will be selected among a list of approximately 300 physicians per country, provided by the Sponsor.

The following selection process will be conducted in each country respectively 12 months and 24 months after Physician received education material:

- A recruitment mail containing the study summary and a participation form will be sent to all Physicians.
- Physicians will be asked to send back the completed participation form to Mapi. Characteristics of physicians, and if applicable, reason for non participation will be collected on the participation form.

- Non-respondent Physicians will be contacted by telephone by Site Monitor Associates (SMAs), trained for this study, to know if they agree or not to participate in the survey and collect their characteristics, and if applicable, the reason for non participation.

9.2.2 Survey conduct

Approximately 60 Physicians per country are expected to participate.

SMAs will present in details the survey and its process to the physicians who agree to participate and will schedule a telephone appointment to complete the survey questionnaire.

Respectively 12 months and 24 months after Eurartesim™ education material is delivered to the Physicians by the Sponsor, the survey questionnaire will be administered by the SMAs by phone to the Physicians selected for the survey and willing to participate.

Close-out mails will be sent to the participating Physicians at the end of the 12-month and 24-month surveys.

9.3 Variables

The following data will be collected:

Physician characteristics:

- Specialty
- Geographic location
- Institution type
- Years in practice
- Number of malaria patients currently treated
- Experience with Eurartesim™ (Number of patients treated the previous year, number of months since last patient treated with Eurartesim™)

Survey questionnaire:

- Date of questionnaire completion
- Knowledge of the drug
- Reception of education material on Eurartesim™
- Indication of Eurartesim™
- Prescription modalities
- Administration modalities
- Effects on cardiac repolarization
- High-risk patients
- Potential side effects
- Awareness of the pregnancy and safety registries
- Information sources on Eurartesim™

9.4 Data Sources

Data will be collected directly from Physicians, through a survey questionnaire administered by phone by SMAs.

The appropriateness and clarity of the survey questionnaire has been tested through qualitative in-depth interviews with a panel of physicians in all participating countries.

9.5 Study Size

Assuming that 20% of Physicians agree to participate in the survey, approximately 60 participating Physicians per country are expected.

As the analyses will mainly comprise calculations of percentages of correct answers, the expected precision obtained for a given percentage has been calculated using the following formula:

$$e = 1.96 \times \sqrt{\frac{p \times (1-p)}{n}}$$

where n = sample size, p = percentage and e = absolute precision.

The following table presents the precision expected with 60 participating Physicians, considering a two-sided confidence interval of 95% and expected percentages ranging from 10% to 50%.

	p				
	10%	**20%**	**30%**	**40%**	**50%**
Precision	7.6%	10.1%	11.6%	12.4%	12.7%
Note: This computation is based on large sample normal approximation					

For clarity, assuming for example an expected percentage equal to 30%, the two-sided 95% confidence interval will extend ±11.6% from the observed percentage.

9.6 Data Management

Each document received at Mapi will be tracked at reception and stamped.

Data entry of data collection forms and questionnaires is double data entry except for free text (single data entry). The two data-entries are independent each other, i.e. without knowing the previous 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.

A Data Management Plan will be prepared by Mapi and approved by the Sponsor before starting the data entry.

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

9.7 Data Analysis

The statistical analysis will be carried out using SAS software version 9.2.

It will be conducted for 12-month and 24-month surveys, separately, on data collected from all participating Physicians and for each country.

A Statistical Analysis Plan will be prepared by Mapi and approved by the Sponsor before the data-base is frozen.

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 and the number of missing data. 95% confidence intervals will be computed on each individual percentage.

Description of the study population:

Characteristics of participating Physicians will be described.

To assess the representativeness of participating Physicians, characteristics of participating and non-participating Physicians will be compared. Reasons for non-participation will be described.

Response to the primary objective:

- Knowledge of indication of Eurartesim™ will be described.
- Knowledge of prescription modalities of Eurartesim™ will be described.
- Knowledge of administration modalities of Eurartesim™ will be described.
- Knowledge of effects on cardiac repolarization will be described.
- Knowledge of high-risk patients will be described.
- Knowledge of potential side effects of Eurartesim™ will be described.

Response to the secondary objectives:

- Awareness of the pregnancy and safety registries will be described.
- Awareness of available information sources regarding Eurartesim™ will be described.

9.8 Quality Control

All sites will be trained by phone on the protocol and study logistics.

The quality control procedures used for data management and statistical analysis will be described in the Data Management Plan and in the Statistical Analysis Plan.

9.9 Bias and Limits of the Study

The main bias identified in this survey is the selection bias.

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

The selection bias that could possibly occur in this study is related to the selection of the participating Physicians.

As inherent in all observational studies, the participation of Physicians is voluntary; some amount of selection bias will therefore be present as Physicians who are better informed may be more liable to participate in the survey.

Given that Physicians participating in pregnancy or safety registries are better engaged with Eurartesim™ risk management activity, the list of approximately 300 Physicians per country, to be used for the present survey, will be separate from the list of Physicians involved in both pregnancy and safety registries.

To characterise the potential selection bias, information about Physicians (Specialty, geographic location, institution type, years in practice, number of malaria patients currently treated, number of patients treated with Eurartesim™ the previous year, number of months since last patient treated with Eurartesim™) will be collected for all contacted Physicians, whether or not they participate in the study. Reasons for non-participation will also be collected. Characteristics of participating and non-participating Physicians will be compared.

10. PROTECTION OF HUMAN SUBJECTS

10.1 Ethical Conduct of the Study

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

10.2 Submissions

10.2.1 Ethics Committee (EC)

Ethical submissions will be performed as required by local legislation in each country involved in the study. The necessary ethical approvals will be obtained for each site before initiation of the site. The study is observational.

10.2.2 Institutional Review Board / Independent Ethics Committee Approval

Submissions and/or notification to the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will be performed as required by local legislation in each country for this type of study.

10.2.3 Data Protection

Physician's personal data shall be treated in compliance with all local applicable laws and regulations.

Data about participating Physicians will be declared and the Physicians will be informed – within the framework of their financial agreement – of their right to access, and correct these data as well as to object, on legitimate grounds, to the processing of these data.

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

10.3 Retention of Physician Records

When the study is completed, the Sponsor will maintain the data collected (questionnaires and databases) for 5 years.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1 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.

Relatedness assessment

The Physician will use the following definitions for any adverse event and 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 Physician for the adverse event.

11.2 AE/ADR reporting

This study is not an organized data collection system on patients treated with Eurartesim™. No patients will be followed-up in this study. However and considering that the objectives of the study consists of measuring the effectiveness of risk management measures, this study qualifies as a PASS study with primary data collection from healthcare professionals.

Consequently and in accordance with EU Good pharmacoVigilance Practices (Modules VI and VIII), reports of ADRs suspected to be related to Eurartesim™ should be reported to competent health authorities. Reports of adverse events should only be summarized in the study report.

During the study period, in the event the Physician is aware of a **serious** AE/ADR in a patient treated with Eurartesim™, the Physician will notify the Corporate Drug Safety of Sigma-Tau **within 24 hours** of the Physician becoming aware of the event, using the SAE Form provided.

The completed and signed SAE form shall be sent 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

Sigma-Tau will be responsible for contacting the reporting Physician to obtain any missing information on the SAE form, to allow it to conform with all international expedited reporting requirements.

It is the Physician'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.

Sigma-Tau pharmacovigilance will be in charge to report individual cases to the concerned health authorities.

Considering the objectives and the design of the study, the reporting of non-serious AE/ADR is not actively solicited in this study. However, and at his/her discretion during the study period, the physician can report suspected non-serious ADR to Eurartesim™ to the Corporate Drug Safety of Sigma-Tau, using the same form and contact details as described above for serious AE/ADR.

11.3 Pregnancy reporting

- Pregnancy are be qualified as a SAE only if it fulfills SAE criteria.
- Abnormal pregnancy outcome in association with Eurartesim™ should be notified on an expedited basis (i.e. within 24 hours of the Physician becoming aware of the abnormal pregnancy outcome). 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.

12. PLAN FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

At the end of the study, Mapi will provide a study report that will be reviewed by the Sponsor. This report will contain a description of the objectives of the study, the methodology, the results and the conclusions of the study. The completed questionnaires 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.

13. REFERENCES

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