A Randomized, Open-Label, Controlled, Multi-Center Study on the Efficacy of a Sustained Release Progesterone Cerclage Cervical Pessary at Doses of 6.3 g or 7.7 g for the Prevention of Preterm Birth and a Maximum Duration of 20 Weeks.

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[redacted]

STATISTICAL ANALYSIS PLAN

Protocol PCP 002 / PHASE II

Multicenter, controlled, open label and randomized study, about the efficacy of a vaginal cerclage pessary with sustained release of progesterone, in doses of 6.3 g or 7.7 g, for the prevention of Premature Birth, with a maximum duration of 20 weeks

Research Product

Cerclage Pessaries containing 6,3 g or 7,7 g of
sustained release of micronized progesterone in each

Prepared for

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CONTENTS

1. INTRODUCTION

This statistical analysis plan is for Andromaco Laboratory S.A., Protocol PCP 002, multicenter, randomized, controlled, open label study to evaluate the efficacy of a vaginal cerclage pessary with a sustained progesterone release, in doses of 6.3 g and 7.7 g for the prevention of premature birth.

The reference materials for this plan include the Clinical Protocol (Version 3, 16 May 2016) and the documents with data specific for the study.

As a background of statistical methods that will be mentioned herein, this sections offers a general vision of the study's objectives and design. It is understood that this is only a summary and that the protocol is the final reference for all the matters discussed as follows.

2. OBJECTIVES

PRIMARY

To evaluate the efficacy of two cerclage pessaries containing 6,3 g and 7,7 g of micronized progesterone of sustained release, in the prevention of premature birth, established through spontaneous delivery after 32 weeks but before 34 weeks of gestation, when the pessary is inserted between week 16 and 24, and removed at 36 6/7 weeks of gestation in pregnant women at risk of premature birth.

SPECIFICS

- Record the occurrence of premature rupture of membranes before weeks 32 and 34 weeks of gestation.
- Evaluation of anatomical characteristics of the cervix in pregnant women: position and length.
- Establish the acceptability and tolerance in pregnant women, with the use of the cerclage pessary.
- Evaluation of local and systemic safety in pregnant women, with the use of the cerclage pessary.

3. STUDY DESIGN

A phase II, efficacy, multicenter, controlled, open label, parallel and randomized exploratory clinical study. It will include singleton pregnant subjects, with history of premature birth and/or short neck and an increased risk of premature birth, who, after reading the informed consent, voluntarily accepted to participate in the study.

For the secondary outcomes, subjects will be their own controls on the following variables to assess: anatomical characteristics of the cervix – position and length; development of surveys in pregnant women to establish the acceptability and tolerance of the intervention; and aspects of local and systemic safety.

Two hundred and seventy +10% pregnant women with risk of premature birth will be enrolled at the participating sites. This population will be divided into 3 groups of treatment with 90 participants each, where control group (A) is with intravaginal capsule of micronized progesterone 200 mg, groups B and C are pessaries with 6.3 g and 7.7 g of sustained release progesterone respectively.

In the prenatal and/or ultrasound control between 16 and 24 weeks of gestation, they will be informed and invited to participate in the study. The inclusion of the volunteers will be in all cases until weeks 24 (0/0) of gestation. The volunteers will be selected on the basis of their clinical history and by trans-vaginal ultrasound performed between 16 and 24 weeks. All volunteers with unique pregnancy and cervical length ≤25 mm but ≥10 mm, will be invited to participate in the study. Prior to inclusion in the study, it is confirmed the vitality of the fetus or other exclusion criteria detailed later. Subjects who refuse to participate in the study will receive the current standard of care in each participating site, according to their condition.

EVALUATION VISITS

The study includes 8 visits to the site. The programmed schedule of assessments for its conduction and the activities to take place in each and one of them are specified in Table 1.

SAMPLE SIZE

The sample size calculation is based on the power to detect differences in the proportion of spontaneous birth between 32 and 34 weeks of gestation, between the formulations of cerclage pessaries with respect to the control group (vaginal progesterone 200 mg capsules). Data collected of at least 90 women in each group will provide at least 80% of the power to detect differences with a rate of 40% or more, using a test of Chi-square of two tails with $\alpha = 0.05$ without correction.

We estimate that up to 10% of the enrolled women may not complete the study, so it must be planned to enroll at least 99 pregnant women in each group to reach at least 198 treated subjects with cerclage pessary and 99 subjects treated with soft capsules of progesterone as a control group (i.e. 99 per each vaginal formulation).

RANDOMIZATION

The randomization will be generated by an independent statistician. The program will be linked in sequential numbers with the code of randomized treatment. A qualified staff member of ANDROMACO laboratory will keep randomization codification, until the database is clean and ready for analysis. The treatment will be dispensed according to the randomization code, the women with unique pregnancy enrolled, will be randomized to receive one of the vaginal formulations of the study.

For the next volunteer, the site will have the next randomization number available. Each woman will receive only the formulation corresponding to the randomization number. The Investigator will record on the log the randomization number and the printed code on each formulation container. Each sites coordinator will assign the randomization code to the volunteers.

Subjects will be randomized to the following three study groups:

- Control Group (A): Intravaginal capsule of micronized progesterone 200 mg on a daily basis.
- Pessary Group (B): Pessary with 6.3 g of sustained release progesterone for a period of around 4 to 5 months.
- Pessary Group (C): Pessary with 7.7 g of sustained release progesterone for a period of around 4 to 5 months.

4. DOCUMENTS AND CHANGE OF VERSIONS

Versión #	Date of Review	Date of Approval	Reason for Change
1.0	05Apr2017		N/A
2.0	21Apr2017		Additions to different sections
3.0	12May2017		English Version and clarification of some issues

CHANGES IN THE PLAN

At the moment there are no changes to the protocol or in the conduction of the study.

5. ANALYSIS CONVENTIONS

The statistical analysis will be made by ILS Clinical Research under the authorization of Laboratorio Andrómaco S.A.

GENERAL PRINCIPLES

The statistical analysis will be provided to give a general summary of the study subjects and a vision of the efficacy and safety of the results. The data provided by the sites will be summarized for this purpose. Tables of absolute and relative frequencies will be constructed for the quality variables. All the percentages will be presented with a decimal. The quantitative variables will be summarized with the number of subjects participating (n), mean, standard deviation (SD), and median, maximal and minimal.

Two tailed test will be carried out for all the analysis and the type I error is 0.05 for continuous variables and the discrete variables. All p values shall be rounded to three decimal and the values under 0.001 will be presented as <0.001 and values greater than 0.999 will be presented as 1.000. A comparison of the treatment groups will be done with respect to the demographic and baseline characteristics using inferential statistical techniques to detect if any of these variables may condition the results in the dependent variables. Comparisons in qualitative variables will be carried out using the Cochran-Mantel-Haenszel (CMH) test of general association, while the comparisons in quantitative variables will be made with a test of comparison of means (ANOVA analysis of variance) for independent samples with normal distribution. In the cases of no normality on the continuous variables, or in case of not belonging to the exponential family for discrete data, the parametric tests will be replaced for nonparametric tests such as Kruskal-Wallis or Friedman. These tests will be presented in each table as deemed necessary. All confidence intervals will be two-tailed and at 95%.

Table 1: Study Schedule of Assessments

Activities	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Final Visit
Demography	X							
Medical History	X							
Physical Exam	X	X	X	X	X	X	X	X
Gynecological Exam	X							
Vital Signs	X	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]
Transvaginal Ultrasound	X	X[2]	X	X	X	X	X	X
Pre-birth Control	X							
Obstetric Background	X							
Lab Tests (Blood and Urine)	X							
Eligibility	X							
Vaginal Discharge	X	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]
Randomization	X							
Pessary Insertion	X							
Acceptability and tolerance to the insertion	X							X
Concomitant Medications	X	X	X	X	X	X	X	X
Evaluation of the Pessary's Adhesion (Groups B and C)		X	X	X	X	X	X	X
Treatment Compliance (Group A)		X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X
Subject's Evaluation		X	X	X	X	X	X	X
Birth[4]								X

1. Pulse and Temperature are added
2. Confirmatory
3. Smear
4. Birth Characteristics: Medication (corticosteroids, antibiotics, tocolysis), hospital admissions; Delivery (Home, Via, interruption); Newborn baby (gender, weight, size, gestational age, head circumference, weight EG, Apgar score); Neonatal complications (infection, respiratory distress syndrome, Intraventricular hemorrhage, Necrotizing Enterocolitis, retinopathy, Blood Transfusion, other); Interventions; Conditions at discharge.

The statistical analysis will be made with SAS software, version 9.2 or greater.

DATABASE MANAGEMENT

The data will be attached to the statistical report. The subjects that will not participate in the analysis (subjects that only completed baseline) will not be included in the tables and figures but they will be included in the listings of data.

6. POPULATION DEFINITIONS

In order to meet the needs of the sub-groups of the Protocol, the following population sub-groups are defined:

Per Protocol (PP): It is defined as the subset of participants who meet the criteria of selection, who expressed their desire to participate in the study, who signed the informed consent form, that the drug has been administered to them and have completed all the visits required or till the termination of the pregnancy as per Protocol.

Intention to treat (ITT): It is defined as the subset of participants who meet the selection criteria, showing their desire to participate in the study, who signed the informed consent form, that the drug has been administered to them, who have at least completed the initial visit and at least one of the subsequent visits to the pessary referred to in the Protocol.

The main efficacy analysis will be carried out with a focus Per Protocol (PP), however it will also be carried out per Intention to Treat (ITT) all the analysis. Otherwise, the main safety analysis will be completed as ITT.

7. SUBJECT DISPOSITION

The subjects that were randomized, completed the study PP and the ITT will be summarized in a table indicating the frequency number and percentage. A CONSORT diagram will be included to observe the availability of subjects in the study.

PROTOCOL DISCONTINUATIONS

The number of subjects and their percentage will be included in the table that includes those subjects that were excluded due to lack of compliance to the requested criteria in the protocol. It is important to identify the subjects that did not conclude the study before the definition of populations to study. Discontinuations to the protocol include: Adverse Events leading to discontinuation, failure to meet inclusión/exclusión criteria, failure to comply with the treatment, failure to comply with the visits, concomitant medication, medical contraindication, voluntary withdrawal of the subjects, death, or others.

8. DEMOGRAPHY AND POPULATION CHARACTERISTICS

Baseline characteristics and demographics will be summarized for PP and ITT population defined in section 2.3.1

Categorical variables will be summarized in tables of frequencies and percentages. Continuous variables will be described by mean, standard deviation, median, max and min.

They will be compared by treatment. For continuous variables a variance analysis (ANOVA) will be used for means comparison for independent samples. Categorical variables will be compared through the test of χ^2 Cochran-Mantel-Haenszel.

Demographic characteristics included age (years), race, weight, height and Body Mass Index (BMI).

MEDICAL HISTORY

The medical history refers to whether the subject presents or presented any relevant conditions (Yes/No), a summary of conditions, diseases or surgical procedures and if these are still active or not. The data will be summarized in tables of frequencies and percentages based on the total number of subjects included in each treatment group and will only be handled for informatory purposes.

PHYSICAL EXAM

The physical exam includes examining body parts such as the abdomen, gallbladder, cardiovascular, endocrine, gastrointestinal and immune system, muscle-skeletal, neurological, psychiatric, respiratory, limbs, head, nose, eyes, ears, lymph nodes and allergies, nutritional facts, scars, skin, thyroid, etc. This will be evaluated in detail at baseline and documented in each visit just if there exist clinical relevance. The information will be summarized in tables of frequencies and percentages based on the total number of subjects in each treatment group and will only be handled for informatory purposes.

VITAL SIGNS

Vital signs consider values of systolic and diastolic blood pressure, heart rate, pulse and temperature. These shall be reviewed as part of the physical examination and the information will be presented in every visit. The information will be summarized in tables with number of participating subjects (n), mean, standard deviation (SD), median, max and min and will only be handled for informatory purposes.

GYNECOLOGICAL EXAM

The gynecological exam includes examination of breasts, external genitalia, vagina, cervix, uterus, other abnormalities, etc. The information will be summarized in tables of frequencies and percentages based on the total number of subjects in each treatment group and will only be handled for informatory purposes.

OBSTETRIC HISTORY

This item considers the history of childbirth in pregnancy, such as premature labor or rupture of membrane, before 35 weeks in preceding pregnancy, with viable fetus. The information will be summarized in tables of frequencies and percentages based on the total number of subjects in each treatment group and will only be handled for informatory purposes.

PREBIRTH CONTROL

This control considers the obstetric formula (GPA), the date of the last normal menstruation and gestational age in accordance with the Date of Last Normal Menstruation (DLNM) and gestational age though Transvaginal Ultrasound in weeks. The obstetric formula will be summarized in tables of frequencies and percentages determined within each group and the gestational ages in the tables with the number of participating subjects (n), mean, standard deviation (SD), median, max and min, and will only be handled for informatory purposes.

LABORATORIES

To be done only at baseline and blood and urine samples will be taken.

INCLUSION AND EXCLUSION CRITERIA

These will be summarized according to the compliance of them. The information will be summarized in tables with frequencies and percentages according to the total number of subjects included in each treatment group and will only be handled for informatory purposes.

9. TREATMENT COMPLIANCE

For Group A, at the start of each visit, it will be recorded the number of capsules dispensed at the previous visit and the number of capsules used, the treatment compliance will be estimated in percentage. The compliance should be between 80 and 120% for each patient.

For groups B and C, it will only be recorded if removal of the pessary was necessary. In this case the subject will be early terminated from the study and the reason for discontinuation will be recorded.

10. EFFICACY ANALYSIS

STATISTICAL HYPOTHESIS

Null Hypothesis:

There is no difference between the methods of cerclage pessaries with a sustained release of 6.3 and 7.7 g of progesterone (Treatments B and C, respectively) with respect to the control method (Treatment A) for at least 20 weeks.

Alternative Hypothesis:

There is a difference between the Control Method (Treatment A) with respect to the one of cerclage pessaries with a sustained release of 6.3 and 7.3 of progesterone for a period of 4 to 5 months.

"There is a difference between the methods of cerclage pessaries with a sustained release of 6.3 and 7.3 g of progesterone (Treatments B and C respectively) with respect to the Control Method (Treatment A) for a period of 4 to 5 months".

PRIMARY ANALYSIS

The primary objective is to evaluate the efficacy of two cerclage pessaries with doses of 6.3 and 7.7 g of sustained release micronized progesterone with respect to the standard treatment of 200 mg of progesterone in capsules administered daily. The primary efficacy analysis will be assessed by comparing the proportions of spontaneous premature delivery after 32 weeks but before 34 weeks of gestation, as primary results, among treatments through the CMH test. Also, the odds ratio and 95% confidence interval will be estimated, considering Group A as the control to be compared with groups B and C. Secondly, the comparison of proportions between the groups C and A will be done with the intention to confirm the significant difference between the highest dose and the standard treatment. Afterwards, the same comparison of proportions will be done with treatment B in order to establish the difference between the group of a minor dose and the standard. Finally the comparison between treatment B and C will be done hoping to demonstrate there is a difference of superiority between B and C where C must be minor than B regarding the number of low-risk pregnancies. The transitivity between treatments will be established according to the results. This is expected to be as follows:

$$Treatment\ C < Treatment\ B < Treatment\ A$$

this is in terms of decrease of the proportion of pregnancies with premature risk. In this way it will determined the effective response to progesterone in the cerclage pessary through the occurrence of spontaneous delivery after 32 weeks but before 34 weeks of gestation. The evaluation of the error type 1 will be with a value of 0.05 for the type of variable being used.

As part of the exploratory analysis for the efficacy of treatments, the risk of spontaneous premature birth from the moment of inclusion in the study until the weeks 32 and 34 of gestation, will be determined with the Kaplan-Meier analysis, where the gestational age is the timeline, spontaneous delivery will be the event and elective deliveries will be censored. A singleton pregnant subject between 16 and 24 weeks of gestation will be eligible to participate in the study when she meets one of the following two conditions:

- Cervical length between 10 to 25 mm and without risk factors
- Cervical length greater or equal to 10 mm and with pre-existing risk factors in the immediate preceding pregnancy characterized by:
    - premature delivery before the week 35 (with a viable fetus)
    - premature rupture of membrane prior to week 35 (with a viable fetus)

There are two ways to measure the gestational age which are the following:

- Gestational Age according to DLNM (weeks)
- Gestational Age according to Transvaginal Ultrasound (weeks)

The time of gestational age will be evaluated through log-rank tests among treatments. The null hypothesis is stated as the no treatment differences in the gestational ages.

Kaplan-Meier (product limit) estimates of the gestational age distribution will be calculated and their corresponding 95% confidence interval (CI) will be presented: 25th percentile, mean, median, and 75th percentile.

The analysis will be performed for the two measurements of gestational time, considering the Transvaginal ultrasound the one most accurate.

For the purposes of this analysis, pregnancies will no longer be considered of high risk in the event birth takes place in week 34 (34 0/7) of gestation or more.

SECONDARY ANALYSIS

For some of the secondary variables, subjects will be their own controls in the following variables to evaluate and the following analysis are proposed:

Occurrence of membranes' ruptures: Premature rupture of membranes after 32 weeks but before 34 weeks of gestation. The Cochran-Mantel-Haenszel (CMH) test will be used, where the incidence of rupture of membranes in each group will be compared and will be identified through the registration of adverse events.

Anatomical cervical changes (Only groups B and C): The length of the cervix and cervical angle variables, will be described as continuous and measured variables through time, using the test of comparison of means through the Analysis of Variance (ANOVA) for repeated measures, considering the baseline result as a covariate in the comparison and shall be based on the sum of squares type III. The difference between groups regarding the change from baseline will be assessed through t tests paired within ANOVA, utilizing the difference in means estimated by least squares. These comparisons will be made amongst all treatment groups with pessary.

Acceptability and tolerability of insertion (only groups B and C):

Acceptability and tolerability will be assessed through a questionnaire which must be completed at the beginning and end of the study. Questions (i) and (ii) are answered at visit 1, question iii (VAS) is answered at visit 1 and final visit, and questions (iv) to (ix) are answered at the final visit.

It is composed of several items

(i) Ease of insertion (visit 1). This question has the following categories: 1 = very good, 2 = good, 3 = regular, 4 = bad and 5 = very bad; and only one of them will be selected.

(ii) Subjects pain at the time of insertion (visit 1). This question has the following categories: 1 = without pain, 2 = with little pain, 3 = with moderate pain, 4 = with intense pain and 5 = with unbearable pain; and only one of them will be selected.

(iii) Visual Analog Scale of pain (VAS) (visit 1 and final visit): this scale is evaluated in 10 points where 10 represents the worst pain suffered during her lifetime and 1 the absence of pain.

Analysis for the VAS will be described as continuous and measured variables through time using the test of comparison of means through the Analysis of Variance (ANOVA) and must be based on the sum of squares type III. The treatment differences regarding the change from baseline, will be assessed through t tests paired within ANOVA, utilizing the difference in means estimated by least squares. These comparisons will be made amongst all treatment groups.

(iv) Expulsion of the Pessary (Yes/No, Final Visit). The date, gestational age of expulsion of the pessary without replacement will be recorded in the log.
(v) Sensation upon the release of the pessary (Final visit). This question has the following categories: 1 = never, 2 = almost never, 3 = occasionally, 4 = frequently, 5 = always; and only one of them will be selected.
(vi) Release of vaginal fluid (Final visit). This question has the following categories: 1 = never occurred, 2 = No changes, 3 = little increase, 4 = big increased 5 = change in color; and only one of them will be selected.
(vii) Sexual intercourse with pessary (Final Visit). This question has the following categories: 1 = better, 2 = as always, 3 = with discomfort, 4 = with pain, 5 = no intercourse; and only one of them will be selected.
(viii) Request for early withdrawal of the pessary (Yes/No, Final visit). The date, gestational age and reason of withdrawal from the pessary will be recorded in the log.
(ix) Recommendation (Yes/No, Final Visit).

For all the above items except number (iii), the information will be summarized in the frequency and percentage tables according to the total number of subjects included in each treatment group and will be handled only for informatory purposes.

Changes in vaginal discharge

Clinical evaluation and/or bacteriological research will take place, infections will be treated with the appropriate antibiotic in case it is confirmed. For these cases, the insertion of a cerclage pessary with sustained-release of progesterone, will take place later at the end of the treatment, but before 24 (0/1) weeks of gestation. It will be monitored in each visit.

In each control, the participant will be asked about the presence, quantity and physical characteristics of the vaginal discharge. To discard presence or absence of infections, the subject will be asked about the need to do a smear of the vaginal discharge for PCR and the need for treatment. The information will be summarized in tables of frequencies and percentages based on the total number of subjects included in each treatment group per visit. A generalized CMH test will be used to assess whether changes in vaginal discharge were different in any of the groups through time.

Children Evaluation

New born will be described in the aspects of demography, physical exam (gestational age), cephalic perimeter, APGAR score, neonatal complications, medical interventions and discharge status. Summary tables of descriptive statistics, absolute and relative frequencies will be included in the analysis only as a descriptive purposes.

11. SAFETY ANALYSIS

11.1 ADVERSE EVENTS

The evaluation of adverse events (AE) will be monitored throughout the study, by direct observation at each visit.

All AE will be recorded (according to the definition), and not only those where the investigator suspects a causal relationship with the treatment. Adverse events of interest; i.e., those in which the investigator at each site must pay particular attention are those that have been defined as local safety (pain, irritation, itching and infection) and major maternal complications attributable to the pessary as chorioamnionitis, severe vaginal or cervical trauma.

All the AE will be encoded in MedDRA version 19.1 or higher to be summarized by System Organ Class (SOC) / Preferred Term (PT).

The following 3 overview tables will be generated by treatment group and overall:

1) Summary of the number and percentage of subjects with at least 1:

- AE
- Serious AE
- Non-serious AE
- Unexpected AE
- Severe AE
- Related AE
- Related serious AE
- AE leading to discontinuation from IMP

The percentage denominator will be the number of subjects in the safety analysis.

2) Summary presenting the number of AEs per subject categorized as 0, 1, 2, 3, 4, 5, and >5;

3) Summary of the number and percentage of AEs for:

- AEs
- Serious AEs
- Non-serious AEs
- Unexpected AEs
- Related AEs
- Related serious AEs
- AEs leading to discontinuation from IMP

The percentage denominator will be the total number of AEs.

11.2 INCIDENCE RATES AND NUMBER OF EVENTS

The incidence of an AE is defined as the number of subjects with occurrence of this AE during the period of interest. The incidence rate (CIR for crude incidence rate) of an AE is defined as the number of subjects with occurrence of this AE during the period of interest divided by the total number of subjects in the respective group (e.g., dose group).

The incidence, incidence rate, the number of events and the percentage of events (related to the total number of events) will be summarized by PT (sorted by decreasing incidence rate in the overall column) for

- AEs
- related AEs
- AEs leading to treatment discontinuation

A separate table per type of AE will be prepared. Only AEs occurring in at least 5% of subjects overall will be included in the text. Tables will be sorted by decreasing incidence overall.

The incidence, incidence rate, the number of events and the percentage of events (related to the total number of events) will be summarized by SOC and PT (sorted alphabetically) for each

- AEs
- serious AEs
- non-serious AEs
- related AEs
- serious treatment related AEs
- AEs leading to treatment discontinuation

For serious AEs, the incidence, incidence rate, the number of events, and the percentage of events will also be presented for serious treatment related AEs, serious fatal AEs and serious fatal related AEs.

For all enrolled subjects, the incidence, incidence rate, the number of events, and the percentage of events (related to the total number of events) will be summarized by SOC and PT(sorted alphabetically) for each.

The number and percentage of events will be summarized by SOC and PT(sorted alphabetically) for the following AE descriptors. Presentation will be for AEs only.

- intensity: mild, moderate, severe
- causal relationship to the imp: related (with subcategories: possible, probable/likely, certain), not related (with subcategories: not related, unlikely), unknown (with subcategories: conditional/unclassified, unassessable/unclassifiable, causal relationship missing)
- outcome: recovered/resolved, recovering/resolving, not recovered/not resolved, recovered/resolved with sequelae, fatal, unknown
- non-IMP related countermeasures: none, newly started medication, others
- action taken with imp: dose not changed, dose reduced, drug interrupted, trial discontinuation, unknown.

Denominator for percentage calculation will be the number of all AEs for the presentation overall SOCs, and the number of AEs per SOC or PT respectively, for the presentation per SOC or PT, respectively.

The following tables will be presented as part of this analysis:

- Table of AE that ended in discontinuation, presented by SOC and PT
- Table of AE presented PT
- Table of serious AE presented PT
- Table of non-serious AE presented PT
- Table of related AE presented PT
- Table of AE related and serious, presented PT
- Table of AE presented SOC and PT
- Table of serious AE presented SOC and PT
- Table of non-serious AE presented SOC and PT
- Table of related AE related, presented SOC and PT
- Table of related and serious AE presented PT
- Table of AE presented SOC and PT and intensity
- Table of AE presented SOC and PT and action taken
- Table of Unexpected AE (non-serious and serious) presented PT
- AEs by primary SOC, PT, and outcome
- AEs by primary SOC, PT and non-IMP related countermeasure
- AES by primary SOC, PT, and causal relationship to IMP

11.3 PREVIOUS AND CONCOMITANT MEDICATIONS

Incidence rates for previous and concomitant medications will be summarized by number of subjects with at least one medication, the naming convention will be codified by Anatomical Therapeutic Classification (ATC) / Therapeutic Chemical Level II.

12. TABLES, LISTINGS AND FIGURES

All the tables, listings and figures will have a complete description of the content, including the name of the company, protocol, population studied and date of elaboration. On the footnote will be indicated the database, program name and output name. All figures will make reference to the tables and listings utilized for their elaboration. All the lists will be ordered by subject number.

Data listings for all data sets will be displayed as an annex to the CSR. Also the following version of the listings will be included:

- Subject completion/discontinuation – all enrolled subjects
- Adverse events leading to trial discontinuation – all enrolled subjects
- Other reasons for discontinuation – all allocated subjects
- Serious adverse events other than death– all enrolled subjects
- Adverse events leading to IMP dose decrease or interruption of IMP – all enrolled subjects
- Adverse events – all enrolled subjects
- Laboratory and vital signs parameters

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