Official Title: The ELTION Study - A Multicenter Open-label Interventional Study of Eltrombopag in Patients With Poor Graft Function After Allogeneic Hematopoietic Stem Cell Transplantation

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The ELTION Study

"A multicenter open-label interventional study of Eltrombopag in patients with poor graft function after allogeneic hematopoietic stem cell transplantation"

Clinical Trial Protocol CETB115EES03

Statistical Analysis Plan for Final Analysis

V1.1

28 September 2020

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LIST OF ABBREVIATIONS

Abbreviation	Explanation
AE	Adverse Event
AESI	Adverse Event of Special Interest
ANC	Absolute Neutrophil Count
CI	Confidence Interval
EPO	Erythropoietin
G-CSF	Granulocyte Colony Stimulating Factor
KM	Kaplan-Meier
OS	Overall Survival
Q1	First quartile
Q3	Third quartile
PT	Preferred Term
SD	Standard Desviation
SOC	System Organ Class

1 INTRODUCTION

The analysis plan proposed below details the necessary aspects to know about the study and the statistical methods to be used to apply them in the final statistical analysis.

2 STUDY OBJECTIVES AND DESIGN

2.1 Study Objectives

Primary objective

To evaluate the efficacy of eltrombopag for poor graft function on overall hematologic response (partial and complete) as determined by platelets, hemoglobin and neutrophil counts, by 16 weeks after the initiation of eltrombopag.

Secondary objectives

1. To determine the response in each hematological lineage separately.
2. To evaluate the long-term efficacy of eltrombopag on overall hematologic response (partial and complete) at 24 and 36 weeks after the initiation of eltrombopag.
3. To evaluate the transfusion independence for red blood cells (RBC) and/or platelets after the initiation of eltrombopag.
4. To evaluate the reduction and discontinuation of concomitant granulocyte colony-stimulating factor (G-CSF) and/or erythropoietin (EPO) therapy.
5. To evaluate the overall survival and survival rate at 24 and 36 weeks.
6. To evaluate the safety of eltrombopag.

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2.2 Study Design

This study is designed as an open-label, single-arm phase II study, in which patients diagnosed with primary or secondary PGF after allo-HSCT will be treated with eltrombopag up to week 36 or until the patient's premature withdrawal. If patient terminates eltrombopag for any of the reasons established in the withdrawal criteria, he/she will be followed for safety up to 30 days after the last dose of eltrombopag, unless he/she withdraws the consent, dies or is lost-to follow-up.

The primary efficacy endpoint is the overall hematologic response rate (partial and complete) by 16 weeks after the initiation of eltrombopag. Eltrombopag will be initiated on day 1 at a dose of 150 mg once daily (75 mg daily in Asian ancestry patients) and will be continued up to 36 weeks.

The study will consist of the following periods:

- Screening Period (baseline): the patient will be invited to participate in the study, after being informed of its characteristics. The patient screening criteria will then be reviewed, and the procedures established in the evaluation schedule will be performed.
- Treatment Period: from administration of the first dose of eltrombopag until time when patient permanently stops taking study treatment for any reason or until 36 weeks have passed.
    - Only patients with a partial or complete response at week 16 will continue to receive eltrombopag until loss of response (defined as a decrease in blood counts to levels that do not continue to meet the criteria for response established in this protocol), unacceptable toxicity, or discontinuation for any other reason.
    - Patients who discontinue eltrombopag because efficacy, will continue in the study and attend the scheduled visits of Treatment Period as per protocol. If loss of response occurs, eltrombopag will be reintroduced at the last effective dose.

  During the Treatment Period, patients will be evaluated weekly during the first month, every 2 weeks during the next 2 months and subsequently every 4 weeks until week 24. For the last 3 months, patients will be followed every 6 weeks.
- Final Visit (or Early Withdrawal): this visit will take place 30 days after completion of the Treatment Period, or premature patient withdrawal.

- Follow-up for Survival: all patients who discontinue from the study, regardless the reason of discontinuation, will be followed for survival for 24 and 36 weeks, unless they withdraw their consent, die or are lost-to follow-up, in which case will be censored at the last contact/follow-up, and study visits will no longer be carried out.

At 36 weeks of the study, the suitability of continuing with eltrombopag will be evaluated by the investigator, and the supply of the drug will be only commercial. Novartis will not supply eltrombopag after the end of the study.

The number of patients planned to be enrolled for the study is 33.

2.3 Study Population

Patients will be eligible for study participation as defined by following inclusion and exclusion criteria:

Inclusion criteria

1. Patient must be able to understand and communicate with the investigator and comply with the requirements of the study and must provide written, signed and dated informed consent form before any study assessment is performed.
2. Male or female patients ≥ 18 years of age.
3. Patients diagnosed with primary or secondary PGF after allo-HSCT defined as two or more cytopenias after day +30 post-transplant (re-tested in a peripheral blood analysis at screening):
   - Platelet count <20,000/ µL (mandatory).
   - Absolute neutrophil count (ANC) <1,000/µL.
   - Hemoglobin < 100 g/L.
4. Presence of donor chimerism >90% in screening visit.
5. Karnofsky status ≥90% (Karnofsky assessment must be performed within 7 days prior to Day 1).

Exclusion criteria

1. Pregnancy statements and contraception requirements:

   Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.

   Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant (or female partners of male patients), unless they are using highly effective methods of contraception during dosing and for 3 months after stopping medication. Highly effective contraception methods include:

   - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
   - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
   - Male sterilization (at least 6 months prior to screening). For female subjects on the study the vasectomized male partner should be the sole partner for that subject
   - Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.

   In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

   Sexually active males unless they use a condom during intercourse while taking the drug during treatment and for 3 months after stopping treatment and should not father a child in this period. A condom is required to be also used by vasectomized men as well as during intercourse with a male partner to prevent delivery of the drug via semen.
2. Evidence of active acute or chronic graft versus host disease (GVHD).
3. Evidence of any active malignancy.
4. Subjects who are human immune deficiency virus (HIV), hepatitis C virus (HCV), hepatitis B surface antigen (HBsAg) positive in screening visit.

5. Cytogenetic abnormality in chromosome 7 present before the allo-HSC.
6. Evidence of any clonal abnormality on cytogenetics (in bone marrow analysis).
   - A local post-transplant conventional cytogenetic assessment should be available within 8 weeks before Day 1.
   - If the cytogenetics is not valuable, i.e, it does not show metaphases, a FISH for MDS-related most frequent abnormalities including chromosome 7 is accepted.

   As a consequence, patients with dry tap bone marrow aspiration are NOT eligible.
7. Evidence of bone marrow involvement or progression of the underlying disease assessed by the applicable methods in each case.
8. Evidence of thrombotic microangiopathy.
9. Evidence of possible causes of cytopenia other than PGF (active infections, myelotoxic drugs, hypersplenism…).
10. Prior use of any thrombopoietin receptor (TPO-R) agonists for PGF.
11. AST or ALT levels >3 x ULN.
12. Creatinine level ≥1.5 x ULN.
13. Total bilirubin level ≥1.5 x ULN.
14. Previous thromboembolic event (other than line-related upper extremity thrombosis)
15. Hypersensitivity to eltrombopag or its components.
16. Clinically significant ECG abnormality history or current diagnosis of cardiac disease indicating significant risk of safety for subjects participating in the study such as uncontrolled or significant cardiac disease or impaired cardiac function including any of the following:

    a). Corrected QTc > 450 msec (male subjects), > 460 msec (female subjects) using Fredericia correction (QTcF) on the screening ECG

    b). Myocardial infarction

    c). Uncontrolled congestive heart failure

    d). Unstable angina

    e). Congenital long QT syndrome.
17. Administration of an investigational drug within 30 days or 5 half-lives, whichever is longer, preceding the first dose of study treatment.
18. Patient with liver cirrhosis.

19. Risk factors for Torsade de Pointes including uncorrected hypokalemia or hypomagnesemia.
20. Subjects with any serious and/ or unstable pre-existing medical, psychiatric disorder or other conditions that could interfere with patient´s safety, obtaining informed consent or compliance with the study procedures as per investigator discretion.

3 STATISTICAL METHODS

Quantitative variables are described with measures of central tendency and dispersion: mean, median, SD, Q1, Q3, minimum and maximum).

Qualitative variables are described using absolute and relative frequencies (N, %). Two percentage columns are presented, total percentage (total %) and valid percentage (valid %), that is, the percentage over the sum of valid responses plus missing values and the percentage over the total of valid responses. When there are not missing values both of them are equal, and then only one will be show.

In the analysis of contingency tables as well as for the comparison of proportions and / or frequency distributions, the chi-square test (or Fisher's exact when appropriate) will be used.

For dependent samples, parametric (t-test paired) or non-parametric (Wilcoxon) statistical tests will be performed depending on the distribution of the sample.

The "time to event" variables (overall survival) will be analyzed using the Kaplan-Meier method.

These tests will be used in all bilateral cases and with a level of significance of 0.05. In cases where a p-value less than 0.05 appears, it refers to the existence of statistical significance.

Data will be analyzed using SPSS v22.0.

4 ANALYSIS POPULATIONS

The populations that will be included in the analysis are defined below:

- The Full Analysis Set (FAS) comprises all patients to whom study treatment has been assigned. All analysis describe in this document, except of AEs analysis (section 9) will be performed with this population.
- The Safety Set (SS) includes all patients who received at least one dose of study treatment. Only AEs analysis (section 9) will be performed with this population.
- Per-Protocol Set (PPS) consists of a subset of the patients in the FAS who are compliant with requirements of the clinical study protocol.

5 SCREENING FAILURES

It will be described the number of screening failure patients. And for these patients, the reason:

- Why was the patient not eligible for enrollment? (Did not meet the inclusion criteria / Did not meet the exclusion criteria / Unacceptable or past medical history-concomitant diagnosis / Intercurrent medical event/ Adverse event / Unacceptable laboratory value(s) / Unacceptable test procedure result(s) / Death / Unacceptable use or excluded medication(s)-therapies / Patient withdrew consent / Physician decisión / Lost to follow-up / Unknown).

In case of “Did not meet the inclusion criteria”, specify the criteria.

In case of “Did not meet the exclusion criteria”, specify the criteria.

6 DESCRIPTIVE ANALYSIS (SCREENING VISIT)

This section will be analyzed with Full Analysis Set population.

6.1 Recruitment Period

The dates of inclusion of the first and last patient will be provided.

6.2 Demography

The continuous variable to be described is:

- Age (years), time from year of birth to year of signed the informed consent.

The categorical variables to be described are:

- Sex (Male / Female). In case of female, Female of childbearing potential? (No / Yes).
- Race (Caucasian / Asian / Black / Other). In case of other, specify.

6.3 Medical history

It will be shown a list with all relevant medical history not related to the study indication

6.4 Underlying disease history

The categorical variable to be described is:

- Diagnosis (Acute myeloid leukemia / Acute lymphoblastic leukemia / Myelodysplastic syndromes / Non-Hodgkin's lymphoma / Hodgkin's lymphoma / Monoclonal gammopathy-Multiple Myeloma / Bone marrow failure-aplastic anemia / Myelofibrosis / Chronic myelogenous leukemia / Chronic myeloproliferative disorders / Others). In case of other, specify.

6.5 Description of the transplant

The continuous variable to be described is:

- Donor age (years).
- Time from transplantation date to start treatment date (months).

The categorical variables to be described are:

- Donor chimerism in peripheral blood (%).
- Donor chimerism in peripheral blood (Total blood / Myeloid compartment).
- Transplant type (Matched family donor / Matched unrelated donor / Mismatched family donor / Mismatched unrelated donor / Haploidentical family donor / Unrelated umbilical cord blood / Other). For every option, it will be describe the family donor (Brother / Sister / Father / Mother / Daughter / Son / Other).
- Source of graft cells (Bone marrow (BM) / Peripheral blood stem cells (PBSC) OBM + PBSC / Umbilical cord blood).
- Poor graft function type (Primary / Secondary).

6.6 Conditioning regimen

It will be shown a multiple response table with the following options:

- Cyclophosphamide
- Fludarabine
- Busulfan
- Melphalan
- Thiotepa
- Body irradiation
- Other

6.7 Cytogenetic

The categorical variables to be described are:

- Has been a local conventional cytogenetics or FISH performed at screening? (No mandatory, there was one available post-transplant (within 8 weeks before Day 1) / Yes).
- Were the cytogenetic results obtained by conventional cytogenetics or by FISH? (Conventional cytogenetics / FISH).
- Results (Negative for clonal abnormalities / Positive for clonal abnormalities)

[redacted]

6.9 ECG evaluation

The categorical variables to be described are:

- Has been the ECG performed? (Yes / No). In affirmative case,
    - Overall interpretation (Normal / Clinically insignificant abnormality / Clinically significant abnormality).
    - Prolongation of QTc-interval (No / Yes).

6.10 Ophthalmologic monitoring

The categorical variables to be described are:

- Has been the ophthalmologic monitoring performed? (Yes / No). In affirmative case,
    - Retin (Normal / Abnormal).
    - Vessels (Normal / Abnormal).
    - Optic disc/nerve (Normal / Abnormal).
    - Cataracts (No / Yes). In affirmative case,
        - Slit-lamp exam performed? (No / Yes). In affirmative case,
            - Slit-lamp exam (Normal / Abnormal).

6.11 Karnofsky performance status

The categorical variable to be described is:

- KPS (100% / 90% / 80% / 70% / 60% / 50% / 40% / 30% / 20% / 10%).

6.12 Anthropometric data / vital signs

The categorical variable to be described is:

- Has been the anthropometric data/vital signs evaluated? In affirmative case, the continuous variables to be described are:
    - Weight (kg).
    - Height (cm).
    - Sitting pulse (beats/minute).
    - Sitting systolic blood pressure (mmHg).
    - Sitting diastolic blood pressure (mmHg).
    - Respiratory rate (breaths/minute).
    - Body temperature (ºC).

6.13 Laboratory evaluation

HEMATOLOGY

The continuous variables to be described are:

- Neutrophils (/µL)
- Platelet count (/µL)
- Hemoglobin (g/L)

In addition, it will be shown:

- Number of patients with <20000 platelets, <1000 neutrophils and <100 hemoglobin.
- Number of patients with <20000 platelets, <1000 neutrophils and >100 hemoglobin.
- Number of patients with <20000 platelets, >1000 neutrophils and <100 hemoglobin.

IMMUNOSUPRESSANTS DRUGS LEVELS

The categorical variable to be described is:

- Has been the Immunosupressants drugs levels performed? (No / Yes). In affirmative case, the continuous variables to be described are:
    - Tacrolimus (ng/mL).
    - CsA (ng/mL).
    - Other (specify).

6.14 Blood smear

The categorical variables to be described are:

- Has been a blood smear performed and analysed for morphological abnormalities? (No / Yes).
- Has been the percentage of schistocytes determined? (No / Yes). In affirmative case, it will be shown the percentage schistocyte (%).

7 END OF STUDY FORM

The categorical variable to be described is:

- Did the patient complete the study? (No / Yes). In negative case, it will be shown a multiple response table with the following options:
    - Adverse event(s). In this case, specify the adverse event.

- Pregnancy.
- Abnormal laboratory value(s).
- Abnormal test procedure result(s).
- Unsatisfactory therapeutic effect.
- Study terminated by sponsor.
- Non compliance with study treatment.
- Protocol deviation.
- Physician decision.
- Subject withdrew consent.
- Lost to follow-up.
- Administrative reasons.
- Death.
- Study indication.
- Other. In case of other, specify.

8 TREATMENT

- Patients with 16 weeks of treatment who discontinue due to no response
- Patients with treatment in week 36.
- Patients with at least one dose modification (No /Yes). For each dose modification, it will be shown the reasons.
- Duration of treatment (days, from the start date to the end date). If the patient has modified the dose, it will be shown the duration for each dose indicated.

9 ADVERSE EVENTS

This section will be analyzed with Safety Set population.

The categorical variables to be described are:

- Number of patients with at least one adverse event.
- Number of adverse events per patient.

For total of adverse events, it will be shown:

- Description of event. The event will be codified by MedDRA and will be shown PT and SOC.
- Does the AE meet the definition of serious? (No / Yes).
- Severity (1 / 2 / 3/ 4/ 5).
- AESI (No / Yes).
- Relationship to study drug (Not related / Related).
- Action taken (No action taken / Study drug dosage adjusted / Study drug temporarily interrupted / Study drug permanently discontinued)
- Outcome (Not recovered-Not resolved / Recovered-Resolved / Recovering-Resolving / Recovered with sequelae / Fatal / Unknown).
- Number of patients with different adverse events reported by severity (1 / 2 / 3 / 4 / 5). A list of the different AEs experienced by patients according to the maximum grade, N and % will be presented. (Events will be run by SOC and PT).

10 OBJECTIVES ANALYSES

In this section, it will be shown the confidence intervals to 95%.

10.1 Primary objective

To evaluate the efficacy of eltrombopag for poor graft function on overall hematologic response (partial and complete) as determined by platelets, hemoglobin and neutrophil counts, by 16 weeks after the initiation of eltrombopag.

It will be calculated:

- The overall response rate, defined as the percentage of patients who have a hematological response (partial and complete) by 16 weeks after the initiation of eltrombopag. If the patient hasn't response in that week because was exit from the study before week 16 and in the last evaluation had a partial or complete response, also be considered as responder.

10.2 Secondary objective 1

To determine the response in each hematological lineage separately.

It will be calculated:

- Percentage of patients who have a partial response in the neutrophil lineage, defined as Absolute neutrophil count (ANC) ≥1,000/ µL (when pretreatment ANC was <1,000/µL) confirmed in two consecutive blood tests separated a minimum of 7 days.
- Percentage of patients who have a complete response in the neutrophil lineage, defined as Absolute neutrophil count (ANC) ≥1,500/ µL (when pretreatment ANC was <1,000/µL) confirmed in two consecutive blood tests separated a minimum of 7 days.
- Percentage of patients who have a response in the neutrophil lineage (partial or complete).
- Percentage of patients who have a partial response in the platelet lineage, defined as Platelet count ≥20,000/µL (with platelet transfusion independence), confirmed in two consecutive blood tests separated a minimum of 7 days.
- Percentage of patients who have a complete response in the platelet lineage, defined as Platelet count ≥100,000/µL (with platelet transfusion independence), confirmed in two consecutive blood tests separated a minimum of 7 days.

- Percentage of patients who have a response in the platelet lineage (partial or complete).
- Percentage of patients who have a partial response in the hemoglobin lineage, defined as Hemoglobin ≥100g/L (when pretreatment Hb was <100g/L) (with red blood cells (RBC) transfusion independence), confirmed in two consecutive blood tests separated a minimum of 7 days.
- Percentage of patients who have a complete response in the hemoglobin lineage, defined as Hemoglobin ≥110g/L (when pretreatment Hb was <100g/L), confirmed in two consecutive blood tests separated a minimum of 7 days.
- Percentage of patients who have a response in the hemoglobin lineage (partial or complete).

Responses in each hematological lineage separately will be determined at weeks 16, 20, 24, 30 and 36 after the initiation of eltrombopag.

In addition,

- To assess if there are statistical significance differences in ANC between baseline and week 24, it will be aplied the appopiate paired test (T-test paired or Wilcoxon, depending the distribution of sample).
- To assess if there are statistical significance differences in ANC between baseline and week 36, it will be aplied the appopiate paired test (T-test paired or Wilcoxon, depending the distribution of sample).
- To assess if there are statistical significance differences in platelets between baseline and week 24, it will be aplied the appopiate paired test (T-test paired or Wilcoxon, depending the distribution of sample).
- To assess if there are statistical significance differences in platelets between baseline and week 36, it will be aplied the appopiate paired test (T-test paired or Wilcoxon, depending the distribution of sample).
- To assess if there are statistical significance differences in hemoglobin between baseline and week 24, it will be aplied the appopiate paired test (T-test paired or Wilcoxon, depending the distribution of sample).
- To assess if there are statistical significance differences in hemoglobin between baseline and week 36, it will be aplied the appopiate paired test (T-test paired or Wilcoxon, depending the distribution of sample).

10.3 Secondary objective 2

To evaluate the long-term efficacy of eltrombopag on overall hematologic response (partial and complete) at 24 and 36 weeks after the initiation of eltrombopag.

It will be calculated:

- Percentage of patients who have secondary overall hematological response at 24 weeks, defined as the maintenance of a partial or complete response at 24 weeks.
- Percentage of patients who have secondary overall hematological response at 36 weeks, defined as the maintenance of a partial or complete response at 36 weeks.

10.4 Secondary objective 3

To evaluate the transfusion independence for red blood cells (RBC) and/or platelets after the initiation of eltrombopag.

It will be calculated:

- The patient receive at least one transfusion before start treatment (No / Yes) (data in section “Supportive Care Record”).
- The patient receive at least one transfusion after start treatment and before week 16 (No / Yes) (data in section “Supportive Care Record”).
- The patient receive at least one transfusion after week 16 and before end treatment (No / Yes) (data in section “Supportive Care Record”).

In each of the studied moments, it will be shown the number of transfusions per patient. In addition, for total of transfusions, it will be shown the type of transfusion (Platelets / RBC).

It will be performed:

- Analysis of contingency tables between number of patiens with transfusions before start treatment and before week 16, using chi-square or Fisher's exact test.

- Analysis of contingency tables between number of patiens with transfusions before start treatment and after week 16, using chi-square or Fisher's exact test.

It will be calculated:

- The period of time where patients did not receive any platelet or RBC transfusions during the treatment period, calculated as the difference between the number of days in treatment and the number of days with transfusions.

10.5 Secondary objective 4

To evaluate the reduction and discontinuation of concomitant granulocyte colony-stimulating factor (G-CSF) and/or erythropoietin (EPO) therapy.

It will be calculated:

- The patient receive EPO at start of treatment (No / Yes) (data in section “Supportive Care Record”).
- The patient receive EPO in visit 6, visit 9, visit 11, visit 13, visit 15 and visit 16 (No / Yes) (data in section “Supportive Care Record”).
- The patient reduce EPO at least 50% from start of treatment to visit 6, visit 9, visit 11, visit 13, visit 15 and visit 16 (No/ Yes) (data in section “Supportive Care Record”).

- The patient receive G-CSF at start of treatment (No / Yes) (data in section “Supportive Care Record”).
- The patient receive G-CSF in visit 6, visit 9, visit 11, visit 13, visit 15 and visit 16 (No / Yes) (data in section “Supportive Care Record”).
- The patient reduce G-CSF at least 50% from start of treatment to visit 6, visit 9, visit 11, visit 13, visit 15 and visit 16 (No / Yes) (data in section “Supportive Care Record”).

It will be realized:

- Analysis of contingency tables between number of patiens who receive EPO at start of treatment and in visit 6, visit 9, visit 11, visit 13, visit 15 and visit 16, using chi-square or Fisher's exact test.

- Analysis of contingency tables between number of patiens who receive G-CSF at start of treatment and in visit visit 6, visit 9, visit 11, visit 13, visit 15 and visit 16, using chi-square or Fisher's exact test.

10.6 Secondary objective 5

To evaluate the overall survival and survival rate at 24 and 36 weeks.

Overall survival (OS), defined as the time from the date of inclusion until the date of death due to any cause, will be calculated using Kaplan-Meier (KM) estimates. The KM graph will show the median OS time and the 95% CI will indicate the number of events and patients censored. All patients who discontinue from the study will be followed for survival for 24, 36 and 40 weeks, unless they withdraw their consent, die or are lost-to follow-up, in which case will be censored at the last contact/follow-up.

The survival rate will also be evaluated by the percentage of patients still alive at 24, 36 and 40 weeks.

10.7 Secondary objective 6

To evaluate the safety of eltrombopag.

This objective has been resolved in this document with:

- Adverse events analysis (see section 9).
- Reason for study withdrawal (see section 7).

[redacted]

[redacted]

[redacted]