Evaluation of perioperative eltrombopag for the management of elective surgery and invasive acts in patients with inherited thrombocytopenia

Evaluation de l'ELtrombopag en Peri-Opératoire lors de chirurgies et actes invasifs programmés chez les patients ayant une Thrombopénie constitutionnelle

ELPOT

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BIOMEDICAL RESEARCH PROTOCOL

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HISTORY OF REVISIONS TO THE PROTOCOL

VERSION	DATE	REASON FOR THE REVISION
01	02/09/2016	
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03	25/09/2017	Review by Pharmacovigilance Unit and Methodology and data management center
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List of abbreviations

ALT Alanine Aminotransferase
CNIL National Commission for Computing and Civil Liberties (CNIL).
CPMP Committee for Proprietary Medicinal Products (European Medical Agency)
CRTC Reference Centre for Constitutional Thrombopathies
DGOS Direction Générale de l'Organisation des Soins
HAS/ANSM High Health Authority/French Agency for the Safety of Health Products
ImT/ITP Immune thrombocytopenia
ISTH International Society of Thrombosis & Haemostasis
IT Inherited Thrombocytopenia
MHEMO Maladies HEMOragiques constitutionnelles network
MYH9 Myosin Heavy Chain 9
PC Platelet Concentrate
SAE Serious Adverse Event
TPO Thrombopoietin
ULN Upper Limit of Normal
WAS/XLT Wiskott Aldricht Syndrom/ X-Linked Thrombocytopenia

1. SUMMARY OF THE RESEARCH STUDY

SPONSOR	*University Hospital Toulouse*
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TITLE	***ELPOT*** *Evaluation of perioperative eltrombopag for the management of elective surgery and invasive acts in patients with inherited thrombocytopenia*
JUSTIFICATION/CONTEXT	*Inherited thrombocytopenias (IT) are heterogeneous groups of rare diseases with spontaneous mild to severe bleeding tendency. The management of invasive procedures at mild or high bleeding risk is an important challenge in IT patients with low baseline platelet counts, when a correction above the recommended threshold safety levels is desirable. Platelet concentrate (PC) transfusion is currently the only treatment, usually effective but, as other blood products, carrying a number of drawbacks and limits.* *In IT resulting from defective megakaryocyte differentiation and/or maturation, or impaired platelet release from mature megakaryocyte in peripheral blood, thrombopoietin mimetics have been shown to increase platelet counts with fully functional platelets and to reduce spontaneous bleeding in most patients, with a good tolerance on short-term administration Eltrombopag is a thrombopoietic agent, primarily licensed in adult and children above 1 yr for the treatment of immune thrombocytopenia (ImT). Short-term use of eltrombopag has been shown to be well tolerated in ImT (adults and children) and limited data in patients with IT indicate that eltrombopag at similar doses is also effective on platelet recovery and spontaneous bleeding and safe.* *The perioperative setting is one of the best conditions to assess the efficiency, safety and usefulness of a haemostatic medicine. Our study will be the first devoted to the management of invasive procedure in IT with a thrombopoietin mimetic.*
OBJECTIVES	*The primary objective of the study is to estimate the response to eltrombopag based on platelet count increase above a safety level of 80 G/L and lack of requirement for PC transfusion for performing invasive acts at mild or high bleeding risk.* *The secondary objective is to document in this particular setting the safety profile of eltrombopag, the kinetics of platelet recovery and the predictive value Inherited thrombocytopenia (IT) type, plasma thrombopoietin (TPO) level and baseline platelet count on the response to eltrombopag.*
DESIGN OF THE STUDY	*Non comparative, interventional, multicentre prospective cohort study evaluating among inherited thrombocytopenia patients, a drug (eltrombopag), already approved for a use among immune thrombocytopenia patients.*
INCLUSION CRITERIA	➢ *Related to thrombocytopenia* • *Symptomatic patients with bleeding history and chronic thrombocytopenia with strong presumption of constitutional origin on the basis of*

	○*the identified mutation and/or* ○*a combination of the following criteria: familial antecedent with Mendelian transmission, duration of thrombocytopenia, suggestive syndromic presentation, and evidence against primary or secondary immune thrombocytopenia, especially absence of immunologic markers and failure of previous conventional or immunosuppressive therapies.* • *Averaged platelet counts during the last five years below the safety level required for the procedure.* ➢ *<u>Related to the procedure</u>* • *Scheduled (>4 weeks) surgery or invasive procedure with anticipated risk of bleeding: e.g. needle biopsy of solid organ (liver, kidney….etc.), interventional endoscopy, major surgeries, or surgery without possibility of mechanical control of haemostasis (e.g. tonsillectomy). For such procedures, prophylactic PC transfusion would be otherwise mandatory.* ➢ *<u>Related to the patient</u>* • *Written informed consent of the patient or his (her) parents or tutors (patients < 18 yrs).* • *Patients included in the national registry of rare platelet disorders (Centre de Référence des Thrombopathies Constitutionnelles-CRTC)* • *Patient with social insurance coverage*
NON-INCLUSION CRITERIA	➢ *Related to thrombocytopenia* • *questionable constitutional origin;* • *definite platelet dysfunction associated to thrombocytopenia (eg: gray platelet syndrome, NBEAL2 and related gene mutations, homozygous Bernard-Soulier Syndrome);* • *thrombocytopenia with predisposition to hematologic malignancies (e.g; RUNX1, ETV6 or ANKRD26 gene mutations).* • *amegakaryocytic thrombocytopenia resulting from mutations in the thrombopoietin TPO-Mpl receptor, supposed, by definition, to be hardly responsive to receptor agonists.* ➢ *Related to the procedure* • *questionable requirement of prophylactic PC transfusions;* • *procedure usually associated with platelet consumption requiring transfusions of PC (e.g.: cardiac surgery), making difficult the evaluation of success or failure;* • *procedures at risk of bleeding with immediate vital or functional consequences (e.g.: intra cranial surgery).* ➢ *Related to the patient* • *age <6 and >75 yrs;* • *personal history of arterial or venous thromboembolic events or known familial thrombophilia;* • *association with another acquired or constitutional hemorrhagic diathesis;* • *chronic hepatitis, cirrhosis, with moderate to severe liver failure (Child-Pugh score ≥5);* • *previous or concurrent myeloid malignancy, including myelodysplastic syndrome;* • alanine aminotransferase (ALT) or bilirubin: - For patients with MYH9-RD: alanine aminotransferase (ALT) or bilirubin levels ≥4 times the upper limit of normal (ULN). - For other patients (non MYH9-RD): alanine

	aminotransferase (ALT) or bilirubin levels ≥2 times the upper limit of normal (ULN). • *altered renal function (creatinin clearance <30 ml/min);* • *pregnancy (negative test required before inclusion in fertile women) or lactating women;* • *breastfeeding.* • *refusal of safe contraception;* • *ocular lenses opacity;* • *hypersensitivity to eltrombopag or one of excipients;* • *previous participation to the present study with invasive procedure performed;* • *current treatment with antiplatelet drugs, anticoagulants or direct acting antiviral agents approved for treatment of chronic hepatitis C infection;* • *psychiatric, social or behavioral condition judged to be non-compatible with the respect of the protocol, including good observance of treatment and compliance to follow-up;* • *adult protected by the law.*
STUDY TREATMENT/STRATEGIES/ PROCEDURES	*Since eltrombopag has never been studied in this indication, we need to estimate the response rate to eltrombopag based on platelet count increase <u>and</u> lack of requirement for PC transfusion. Control groups treated with PC transfusion or placebo as comparator, or historical comparison would have no sense, since by definition 100 % of procedures will be at risk of bleeding and require correction of platelet counts above predefined safety levels.* *Eltrombopag (Revolade® Novartis) is an oral, small non-peptide molecule which binds to the TPO receptor. Eltrombopag produces a sustained increase in platelet count after 8 days, reaching a maximum at 3-4 weeks and returning to baseline 1-2 weeks following discontinuation. The usual dose for primary ImT in adults and children above 6 yrs is 50 mg/day with adjustment to 75 or 25 mg/day according to the platelet response.* *Accordingly, after the inclusion visit, eltrombopag will be prescribed at the standard dose of 50 mg/day with dose adjustment on the platelet count (+/- 25 mg) after 2 weeks, for a maximum of 4 weeks before an invasive procedure. If the predefined safety level of platelet count required for the procedure has been reached, the treatment will be discontinued and the patient will be operated without prophylactic transfusion of PC, otherwise mandatory. Clinical and biological follow-up will be performed until the end-of–study visit, 4 weeks after the intake of the last tablet of eltrombopag.*
JUDGEMENT CRITERIA	*<u>Primary:</u> Full response ("success") is defined as an increase in platelet count above the safety level of 80 G/L measured on the day before procedure <u>and</u> a procedure performed without PC transfusion,* *<u>Secondary:</u> Adverse effects recorded during treatment and the 4-week follow-up after discontinuation, including excessive bleeding or any complication related to bleeding or thrombotic events.* *Serial platelet counts and change in platelet size.*
SIZE OF THE STUDY	*This study addresses a relatively rare event in rare patients. The population candidate ITs is around 300 in France, a number maybe underestimated since these patients may remain undiagnosed for long. Referral for advice before an invasive procedure and severe thrombocytopenia is a usual mode of discovery of new IT patients. Participating centers (n= 25) belong*

	to a national network (MHEMO) dedicated to the management of constitutional hemorrhagic diseases. We estimate 1-3 patients eligible per center during the trial period. Accordingly, a number of 25 inclusions is realist. About 1/3 of candidate patients are expected aged 6-17 yrs and eltrombopag will be proposed on the basis of dedicated trials in children with ImT. *This sample of 25 patients is in accordance with the number of patients usually included in early phase II trials (small number of diseased patients), and in pilot studies.*
NUMBER OF CENTRES PLANNED	*25*
DURATION OF THE STUDY	*Duration of the inclusion period 48 months* *Duration of each patient's participation 8±1 weeks* *Total duration of the study 54 months*
STATISTICAL ANALYSIS OF THE DATA	*The sample of patients included in this study will first be described using usual descriptive statistics.* *The primary endpoint (success rate after eltrombopag administration) will be the percentage of patients who will not require PC transfusion before (i.e: platelet count above the safety level of 80 G/L), during, or after the invasive procedure. A 95% confidence interval will be provided.* *Secondary categorical endpoints will also be assessed with a 95% confidence interval. The distribution of secondary continuous endpoints will be described by providing median, interquartile range, and extreme values. If the distribution is in accordance with a normal distribution, mean and standard deviation will also be provided. The kinetics of platelet recovery will be described for each patient by graphically drawing platelet count according to time. A paired T-test or a paired ranked test will be used to assess changes in laboratory parameters after eltrombopag administration. The potential predictive value of baseline serum thrombopoietin level to predict platelet response will be studied without and with adjustment for one or two main potential confounding variables such as age, or gender. The same analysis will be performed to assess the predictive value of baseline platelet count (i.e. measured at inclusion) on the response to eltrombopag.*
EXPECTED CONSEQUENCES	*Thrombopoietin mimetics directly target a mechanism of thrombocytopenia with few off-target effects. Invasive acts at risk of bleeding are a major concern in IT patients. Should the results of the study be positive, eltrombopag (one oral tablet/day for 3-4 weeks) could be proposed to IT patients for elective surgery and other invasive procedures, avoiding the transfusion of PC in a large majority of them.*

2. SCIENTIFIC JUSTIFICATION AND GENERAL DESCRIPTION

2.1. CURRENT STATE OF KNOWLEDGE

- Rationale of the disease.

Thrombocytopenia is defined by a number of blood platelets below the limit of normal (usually 150 G/L). Platelets are key players in hemostasis by forming within minutes plugs on wounded vessels, in cooperation with the coagulation system. Thereby, platelets prevent blood loss from the vasculature, especially in the microcirculation. Accordingly, a numerical defect of platelets exposes the patients to spontaneous or provoked (trauma, surgery) bleeding. The severity and incidence of bleeding are roughly in inverse proportion with the platelet counts. Most of thrombocytopenia are acquired during the life. They appear at any age, because of hematological malignancy, immune destruction, or drug toxicity. In contrast, inherited thrombocytopenia (IT) are genetic diseases, and the symptoms usually appears very early, sometimes in neonates. The treatment of IT is currently limited to the administration of platelet concentrates prepared from blood donors, in the event of severe bleeding or anticipated risk of bleeding (e.g. invasive acts).

- Inherited thrombocytopenia (IT)

Inherited thrombocytopenias are heterogeneous rare diseases with spontaneous mild to severe bleeding tendency (1). Pathogenic mechanisms of IT include defective megakaryocyte differentiation and/or maturation, impaired platelet release from mature megakaryocyte in peripheral blood, by far the most frequently diagnosed in adults or increased platelet consumption. ITs include syndromic disorders, in which thrombocytopenia can associate with other clinical features, and non-syndromic forms, in which the platelet defect is the only manifestation of the disease. Knowledge in the field of ITs has remarkably improved over the recent years (2), due to the development of next-generation sequencing technique, but it can be estimated that the known gene mutations still account for less than 50 % of IT (3).

- Thrombopoietin (TPO) and TPO mimetics

Thrombopoietin is a hormone constitutively produced by the liver which regulates platelet production by binding to and activating TPO receptor on the megakaryocyte cell surface, thereby inducing intracellular signalling cascade that leads to increased platelet production (4). By analogy with erythropoietin in anaemia, the therapeutic use of TPO in a wide variety of thrombocytopenia had a strong rationale (5), but recombinant thrombopoietins were discontinued early in their clinical development due to the induction of drug antibodies, and second generation of exogenous thrombopoiesis-stimulating agents, “TPO mimetics’ without sequence homology with endogenous TPO, have been designed.

Two TPO mimetics are currently licensed for the treatment of primary immune thrombocytopenia and related disorders (6): Romiplostim (Nplate®, Amgen), a recombinant fusion protein “peptibody”, and eltrombopag (Revolade®, Novartis), a non-peptide small molecule. Both drugs bind to the TPO receptor on megacaryocytes, resulting in activation of signalling cascade (JAK-STAT and MAP kinase pathways) and

increase platelet production. The former is available for subcutaneous administration and the latter in tablets for oral administration.

- TPO mimetics in inherited thrombocytopenia

TPO mimetics are not licensed for IT treatment. Pre-clinical and preliminary clinical data suggest that in IT resulting from defective megakaryocyte maturation, platelet release or reduced life-span, eltrombopag or romiplostin could be effective in a majority of patients with various forms of IT (7). The largest published study reports the effect of eltrombopag in 12 patients above 16 yrs of age with MYH9-type macrothrombocytopenia (8). After 3 weeks at the eltrombopag dose of 50 mg daily, 3 patients achieved platelet counts of ≥150 G/L, 2 patients between 100 and 150 G/L, 3 between 50 and 100 G/L and 4 remained <50 G/L. The 7 patients with less than 100 G/L received eltrombopag 75 mg daily for further 3 weeks and 4 remained below 50 G/L. There was no safety concern. Spontaneous bleeding diathesis quickly improved in all symptomatic patients responder to the drug. *These results were recently confirmed in a retrospective study of 24 patients with various types of IT (9). The authors conclude that in most patients, short-term administration of eltrombopag increased platelet count above the threshold for major surgery recommended by current guidelines, and that both short- and long-term (3 and 16 weeks respectively) treatments were globally well tolerated.* In another study performed in 8 patients with Wiskott-Aldrich syndrome and X-linked microthrombocytopenia (mainly children, age 6.9 ± 2.7 m±sd), 5 patients who were on eltrombopag treatment for at least 1 month were clinical responders, as evidenced by achieving at least one platelet count ≥ 50 G/L and double the baseline count, and 6 of 8 had reduced bleeding symptoms without inducing platelet activation (10). No patients experienced drug-related serious adverse events on eltrombopag. The experience published with romiplostim is limited to a single case study (11).

To sum up, limited data in patients with ITs indicate that relatively short-term (weeks) treatment with eltrombopag at a daily dose ≤75 mg increases platelet counts and reduces bleeding in a significant proportion of patients, without major safety concern. The management of invasive procedure is an important challenge for IT patients with low platelet counts, the only treatment being presently the transfusion of platelet concentrate (PC). Our trial is designed to evaluate eltrombopag as an alternative to PC transfusions in this particular condition.

2.2. HYPOTHESES OF THE STUDY AND RESULTS EXPECTED

Our hypothesis is that preoperative treatment by a TPO mimetic will be effective and safe and will avoid requirement of PC transfusion in a majority of IT patients. Invasive acts at risk of bleeding are a good condition for assessing the effectiveness of the drug, since bleeding almost invariably occurs in the absence of intervention, is easily to record, and can be rescued by transfusion of PC in case of failure of the treatment.

In patients with baseline platelet counts <50 G/L, a correction above the recommended threshold safety levels (from 50 G/L to 100 G/L depending on the type of procedure) is desirable in a large set of invasive acts (see 12 for the French National Guidelines for good clinical practice “Transfusion de Plaquettes,

produits-indications"). Contrarily to ImT which could benefit of other therapeutic approaches, the only effective treatment in IT is the transfusion of PC. PC are usually effective but, as other blood products, carry a number of drawbacks and limits (see § 2.4).

Short-term use of eltrombopag has been shown to be well tolerated in ImT (13) and IT patients (8-10) Based on available data in IT, a 4-week treatment is usually required to obtain the expected platelet counts in responder patients. Accordingly, the study will be restricted to scheduled procedures, short-term use, IT without severe biological evidenced platelet dysfunction and baseline platelet counts below the safety levels required for the procedure, for which transfusions of PC would have been otherwise mandatory.

2.3. REASONS FOR THE METHODOLOGY CHOICES

This is a prospective cohort open labelled, multicentre study, with no comparative arm. There is no reference treatment arm in the trial since PC transfusion, presently the only alternative for safety procedure, will be a criterion of failure of treatment. There is no placebo arm since a spontaneous correction of thrombocytopenia is very unlikely.

The strengths of the project are collective effort, definite indicators and foreseeable benefit for the patient.

- Collective effort (population size)

Due to the rarity of the pathology and of the condition (invasive act at risk of bleeding), recruitment should be based on a very large basis. The MHEMO network, recently approved by the DGOS for the diagnosis and treatment of constitutional hemorrhagic diseases (Willebrand/Hemophilia/Platelet disorders) provides a national platform for such a trial.

- Definite indicators (judgement criteria)

The primary judgement criterion is the increase of platelet count up to the predefined safety level (80 G/L) and performance of an invasive procedure in safe conditions without requirement of PC transfusion during all the study period until the end-of study visit. This criterion is clear and objective.

Bleeding is not part of the primary judgment criteria for several reasons. Mild/moderate bleeding is usual in the invasive acts selected in the trial, in which a body cavity is entered, mesenchymal barrier crossed, facial plane opened or normal anatomy altered. Conversely, excessive -"major"- bleeding is unusual, but its definition is not exempt of subjectivity and ISTH criteria are only valid for studies performed in double blind (14). In patients with inherited thrombocytopenia, excessive bleeding has been estimated to occur in 15 % of major surgeries (15). This value however could not be used as comparator in our trial since, in the only retrospective survey available (14), platelet transfusion alone as prophylactic treatment was not associated with a lower frequency of major bleeding, compared to patients who received no prophylaxis (16). This unexpected result may be attributed to a patients' selection bias, to the origin of bleeding, which may be only partially dependent of defective haemostasis, or/and to the absence of robust recommendations for platelet transfusions in perioperative setting (16). As bleeding is a major concern, it will be assessed as a serious adverse event, secondary endpoint, both locally (judgment of the site investigator), and centrally (adjudication by an independent Event validation committee, see below §12).

➢ Foreseeable benefit for the patient

The direct benefit for the patient is having an invasive act at bleeding risk without PC transfusion, (§2.4). Of note, such procedures in childhood are relatively frequent and may represent one third of eligible patients in the present research project. The two large placebo-controlled studies performed in primary ImT (17,18) indicate that eltrombopag has both good efficacy and a good safety profile in children, which led to its approval for children >6 years in United States and >1 years in Europe (see 18 for a review).

2.4. BENEFIT/RISK RATIO

The benefit of eltombopag for the patient is to have an invasive procedure performed safely with endogenous platelets, instead of allogenous platelets (PC transfusion) in standard treatment. Limited data (§ 2.1) indicate that endogenous platelets after TPO mimetics in inherited thrombocytopenia are efficient and therefore that the invasive procedure will be performed in the same conditions of safety with respect to bleeding as with PC administration.

➢ About the standard treatment with PC

Recent data provided by the HAS/ANSM (11) indicate a low, but significant due to its high case-fatality, risk of bacterial infection transmitted by the PC (n=7 en 2012) and a very low residual risk of viral transmission (one hepatitis E Virus). Depending on the type of platelet concentrate, the following adverse events of grade 2 or 3 par 10^5 units transfused reported to the French National Pharmacovigilance database varies between 50-80 for allo-immunisation anti-erythrocytes, 30-40-for non-hemolytic fever and 11-20 for allergic reactions. A more specific adverse event of PC is the risk of allo-immunisation anti-HLA making the patient refractoriness to future platelet transfusions and with potential fetal burden. Finally, platelet storage in blood bank induces changes in morphology and function, which may alter their function or survival in the recipient.

Another limitation is the refuse of blood-derived products by the patient for religious reasons.

Therefore, although patient bleeding from thrombocytopenia most likely benefit from PC transfusion, an alternative without transfusion is desirable.

➢ About the study treatment

The experience of adverse effects in IT patients is very limited. In the MYH9-type IT (12 patients, max 6 weeks of treatment) eltrombopag was well tolerated in all cases, with only 2 patients reporting mild and transient headache and 1 patient suffering from transient dry mouth at the beginning of treatment. The only blood parameter that changed during treatment was platelet count (8, 9). In WAS/XLT patients (10), there was no adverse event reported with the exception of one transient mild elevation of serum ALT levels in a patient who continued on therapy.

The experience is largest in patients with chronic immune thrombocytopenia (20 and SCP, ref 21):

- In 4 controlled and 2 uncontrolled clinical studies, 530 chronic adult ITP patients were treated with eltrombopag. The mean duration of exposure to eltrombopag was 260 days. The most important serious adverse reactions were thrombotic/thromboembolic events. The most common adverse reactions occurring in at least 10% of patients included: hepatobiliary laboratory abnormalities, headache, anaemia, decreased appetite, insomnia, cough, nausea, diarrhoea, alopecia, pruritus, myalgia, pyrexia, fatigue, influenza-like illness, asthenia, chills and peripheral oedema.
- In 2 controlled clinical studies, 157 chronic paediatric ITP patients were treated with eltrombopag (17-18). The median duration of exposure was 171 days. With the exception of thromboembolic event which was not observed in children, the profile of adverse reactions in paediatric ITP patients 1 year and older was comparable to that seen in adults. The most common adverse reactions (≥ 3% and greater than placebo) were upper respiratory tract infection, nasopharyngitis, cough, diarrhoea, pyrexia, rhinitis, abdominal pain, oropharyngeal pain, toothache, rash, increased AST and rhinorrhoea. Accordingly, eltrombopag is licensed for children above 1yr.

The above incidences of adverse events in ITP are reported for relatively long-term exposure. The annual incidence of thromboembolic events is between 2.5 to 3.2 /100 patient-year, without apparent change with the length of the study (see 22 for a review), corresponding to a risk of <3/1000 patients for the duration of our study.

Hepatobiliary laboratory abnormalities were found in about 10 % of adult patients (20, 21). For the majority of those (25/29 in the EXTEND study), these abnormalities resolved upon continuing treatment or after discontinuation, whereas 4 with laboratory abnormalities elevated at baseline had intermittent elevations throughout the study (20). Similarly, hepatobiliary laboratory abnormalities in children were mostly mild, reversible, and not accompanied by clinically significant symptoms that would suggest impaired liver function (17, 18).

In clinical practice in unselected patients, similar results as in the phase III trials were reported (24). In this study, of 152 patients, 28 (18.4%) experienced one or more adverse events during treatment, with a total of 66 mainly grade 1–2 adverse events. The most common adverse effects reported were diarrhea and headache. Seven patients (5.0%) had hepatobiliary laboratory abnormalities, resolved for 6 despite continued treatment and 1 after discontinuation. Discontinuation for intolerance occurred in about 5% (7/132) patients having achieved a complete platelet response.

Taken together, with the careful selection of our study population, the short duration of treatment and the close monitoring of our patients, the safety profile of eltrombopag is acceptable and balances favourably the risks of PC transfusions.

2.5. EXPECTED CONSEQUENCES

The perioperative setting is one of the best conditions to assess the efficiency, safety and usefulness of a haemostatic medicine. Our study will be the first devoted to the management of invasive procedure in IT with a thrombopoietin mimetic. Published data in the perioperative setting, initially limited to 3 short case reports, 3 with eltrombopag (25-27) and one with romiplostim (28), were encouraging because all

successful and well tolerated, but with potential publication bias. *A series of 5 patients (12 procedures) recently published reports a full success in 4 patients (11 procedures) and a failure in 1 (29 Zaninetti 2019) and confirms this favourable trends.*

Invasive acts at risk of bleeding are a major concern in IT patients but this represents a small public health burden because of the rarity of disease. Should the results of the study be positive, eltrombopag (one oral tablet/day) for 3-4 weeks) could be proposed to IT patients for elective surgery and other invasive procedures, avoiding the transfusion of PC in a large majority of them. A study in children <6 years of age should then be discussed.

3. OBJECTIVES OF THE STUDY

3.1. PRINCIPAL OBJECTIVE

The primary objective of the study is to evaluate the proportion of patients with IT who, upon preoperative eltrombopag treatment, will reach a pre-specified safety level of platelets before, and will not require a PC transfusion before, during, or after an elective invasive procedure at mild or high risk of bleeding.

The working hypothesis is that 4-week treatment with eltrombopag increases the platelet count to safety levels for the procedure and that newly produced platelets are fully functional.

The study population is severe IT patients planned for an invasive procedure at risk of bleeding for which preoperative PC transfusion would be otherwise mandatory. Therefore the study is non-comparative and non-randomized.

Accordingly, the treatment by eltrombopag will be rated "successful", if the two objective criteria below are both fulfilled:

- an increase in platelet count ≥80 G/L on the day before the procedure, avoiding preoperative PC,
- and a procedure performed without transfusion of PC at any time until the end of follow-up.

Should one or both criteria be not fulfilled, the treatment by eltrombopag will be rated as "failure".

3.2. SECONDARY OBJECTIVES

- The first secondary objective is the safety profile of eltrombopag: Number, percentage, severity and type of adverse events during the treatment and the 30 days following the intake of the last tablet.
  These adverse events may be;
  - related to this particular setting (risk of perioperative bleeding or vascular thrombosis).
  - or more generally, all adverse events reported during the clinical trials in primary ImTs (see § 2.4) or previously unreported (i.e.: unexpected).

  Our hypothesis is that short-term treatment with eltrombopag will be well-tolerated, efficient (no excess of unusual bleeding) and well-accepted by the patients.

Other secondary objectives are to document

- the minimal dose of eltrombopag and the time required to obtain the safety level of platelet counts;

- the kinetics of platelet recovery before the procedure and of return to baseline in the postoperative period;
- the effect of treatment on some laboratory parameters related to platelet production and function (changes in platelet size in IT with macro- or micro-thrombocytopenia and predictive value of plasma TPO level and baseline platelet count on the platelet response).

4. CONCEPTION OF THE STUDY

- This is a non-comparative, interventional, multicenter prospective cohort study evaluating among inherited thrombocytopenia patients, a drug already approved for a use among immune thrombocytopenic patients, including children (see Appendix III).
- The test drug is eltrombopag (preferred to romiplostim for its largest clinical published experience in IT patients, see §2.1).
- The risk level of bleeding of the most frequent invasive procedures will be estimated using current guidelines (30-3). As the distinction between mild and high risk of bleeding is arbitrary and not uniform in the literature, and as a procedure initially rated as mild risk may turn to high during the surgery, the same safety level of 80 G/L for both was chosen for the present trial, in accordance with the French National Guidelines for Platelet Transfusion (12). Procedure at risk of bleeding with immediate vital or functional consequences will be not included (§ 5.2.2)
- The study is largely multicentre for having a chance to enrol the expected number of 25 cases. All centres are specialized in the management of patients with haemorrhagic diathesis through the MHEMO network.
- All visits and consultations will be performed by one of the co-investigators identified in each center. The chart-flow of the study includes out-patient consultations for screening and inclusion, in-patient visit(s) in the mid of preoperative period and, after discharge, out-patient consultation for end of study, with a weekly telephone call follow-up and biological monitoring in the preoperative and postoperative weeks.
- Monitoring will be performed by a staff experimented in clinical research and coordinated by a steering committee of 8 co-investigators (§ 12). The rules for arrest of the treatment in individual patient have been predefined (§ 9.7).
- An independent Event Adjudication Committee (EAC) will analyze all serious adverse events, as soon they are reported, especially bleeding judged of unusual abundance requiring rescue PC administration or suspected or confirmed thromboembolic events. The conclusions of the committed will be immediately forwarded to the steering committee.
- An independent Data Safety Monitoring Board (DSMB) will review periodically the data and provide the steering committee with advice on trial arrest, interruption or changes in the inclusion/non-inclusion criteria if necessary. Any change will be submitted to the “Comité de Protection des Personnes”.
- Data management and analysis will be performed by the Methodology Unit of the Toulouse University Hospital.

5. ELIGIBILITY CRITERIA

5.1. INCLUSION CRITERIA

5.1.1 Related to thrombocytopenia

- Symptomatic patients with bleeding history and chronic thrombocytopenia with strong presumption of constitutional origin on the basis of
  - the identified mutation and/or
  - a combination of the following criteria: familial antecedent with Mendelian transmission, duration of thrombocytopenia, suggestive syndromic presentation, and evidence against primary or secondary immune thrombocytopenia, especially absence of immunologic markers and failure of previous conventional or immunosuppressive therapies.
- Averaged platelet counts during the last five years below the safety level required for the procedure.

5.1.2 Related to the procedure

- Scheduled (>4 weeks) surgery or invasive procedure with anticipated risk of bleeding: e.g. needle biopsy of solid organ (liver, kidney….etc.), interventional endoscopy, major surgeries, or surgery without possibility of mechanical control of haemostasis (e.g. tonsillectomy). For such procedures, prophylactic PC transfusion would be otherwise mandatory.

5.1.3 Related to the patient

- Written informed consent of the patient or his (her) parents or tutors (patients < 18 yrs).
- Patients included in the national registry of rare platelet disorders (Centre de Référence des Thrombopathies Constitutionnelles-CRTC)
- Patient with social insurance coverage

5.2. NON-INCLUSION CRITERIA

5.2.1 Related to thrombocytopenia

- questionable constitutional origin;
- definite platelet dysfunction associated to thrombocytopenia (eg: gray platelet syndrome, *NBEAL2* and related gene mutations, homozygous Bernard-Soulier Syndrome);
- thrombocytopenia with predisposition to hematologic malignancies (e.g; *RUNX1, ETV6* or *ANKRD26* gene mutations).
- amegakaryocytic thrombocytopenia resulting from mutations in the thrombopoietin TPO-Mpl receptor, supposed, by definition, to be hardly responsive to receptor agonists.

5.2.2 Related to the procedure

- questionable requirement of prophylactic PC transfusions;
- procedure usually associated with platelet consumption requiring transfusions of PC (e.g.: cardiac surgery), making difficult the evaluation of success or failure;

- procedures at risk of bleeding with immediate vital or functional consequences (e.g.: intra cranial surgery).

5.2.3 Related to the patient

- age <6 and >75 yrs;
- personal history of arterial or venous thromboembolic events or known familial thrombophilia;
- association with another acquired or constitutional hemorrhagic diathesis;
- chronic hepatitis, cirrhosis, with moderate to severe liver failure (Child-Pugh score ≥5);
- previous or concurrent myeloid malignancy, including myelodysplastic syndrome;
- alanine aminotransferase (ALT) or bilirubin:
    - For patients with MYH9-RD: alanine aminotransferase (ALT) or bilirubin levels ≥4 times the upper limit of normal (ULN).
- - For other patients (non MYH9-RD): alanine aminotransferase (ALT) or bilirubin levels ≥2 (ULN).altered renal function (creatinin clearance <30 ml/min);
- pregnancy (negative test required before inclusion in fertile women) or lactating women;
- refusal of safe contraception;
- breastfeeding.
- ocular lenses opacity;
- hypersensitivity to eltrombopag or one of excipients;
- previous participation to the present study with invasive procedure performed;
- current treatment with antiplatelet drugs, anticoagulants or direct acting antiviral agents approved for treatment of chronic hepatitis C infection;
- psychiatric, social or behavioral condition judged to be non-compatible with the respect of the protocol, including good observance of treatment and compliance to follow-up;
- adult protected by the law.

5.3. METHODS OF RECRUITMENT

This study addresses a relatively rare event in rare patients. The population of patients with one of candidate ITs is around 300 in France. This number may be underestimated since these patients, as usual in rare diseases, may remain not diagnosed if they have no spontaneous severe bleeding symptoms. On the other hand, the need of invasive act at risk of bleeding is not very superior in these patients compared to the general population.

Recruiting centers are members of the network MHEMO. The list of co-investigators (Appendix I) covers practically all the French metropolitan territory. All 25 centres have an excellent experience in the management of haemorrhagic diathesis in adults and children, and are used to coordinate their action with concerned doctors (anaesthesiologists, surgeons and others).

The mode of recruitment will be referral for advice before an invasive procedure face to a severe thrombocytopenia. This is a frequent cause of consultation in the MHEMO centers for already diagnosed IT patients with regular follow-up, as well as for new IT patients diagnosed on this occasion. This visit will be

the screening visit (§ 9.3). Reasonably, the intended period for accepting inclusions is about 3-5 days and the inclusion visit (§ 9.4) in the centre can be planned one week later.

On the basis of individual interviews, we forecast 1-3 patients eligible per centre. Due to the selection criteria and the constraints of a clinical trial, the inclusion rate is estimated to be 1:2 and the chance for each centre to include during the trial period is between 0 and 2 case(s). Of note, to avoid a bias in favour of the treatment, a same patient will be able to participate only once in the study (previous participation is a non-inclusion criterion).

6. STUDY TREATMENT/STRATEGIES/PROCEDURES

6.1. TREATMENT STRATEGY

About eltrombopag

Eltrombopag olamine [3′-{*N*′-[1-(3,4-Dimethyl-phenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene] hydrazine}-2′-hydroxybiphenyl- 3-carboxylic acid] is a small (MW: 546 D) molecule acting as orally available non-peptide agonist of the TPO receptor.

Eltrombopag interacts with the transmembrane domain of the human TPO receptor and initiates signalling cascades inducing proliferation and differentiation from bone marrow progenitor cells.

The trade name of eltrombopag is **Revolade®,** released in EU by NOVARTIS Pharma S.A.S. Revolade® is available in two dosages: 25 and 50 mg film-coated tablets. Eltrombopag is currently approved for the treatment of:

- chronic immune (idiopathic) thrombocytopenic purpura (ImT) patients aged 1 year and above who are refractory to other treatments. Eltrombopag has been approved for the treatment of ImT (ASMR II) since 2010.
- adult patients with chronic hepatitis C virus infection for the treatment of thrombocytopenia, where the degree of thrombocytopenia is the main factor preventing the initiation or limiting the ability to maintain optimal interferon-based therapy
- adult patients with acquired severe aplastic anaemia who were either refractory to prior immunosuppressive therapy or heavily pre-treated and are unsuitable for haematopoietic stem cell transplantation.

The main relevant interaction in the context of the study is with HMG-CoA reductase Inhibitors. In case of co-administration, the dose of statins should be reduced and the patient should be monitored for the occurrence of symptoms indicators of an adverse event of the statins.

The complete list of adverse events can be found are listed on the latest SCP, updated May 26th 2016 (21) and the most relevant ones have been summarized on § 2.4

Elevation of hepatobiliary markers during treatment, usually mild and without sign of liver impairment, is one of the most frequent adverse event and usually resolves spontaneously on treatment or after discontinuation. As a precaution for use, patients with known liver pathology or baseline ALT and bilirubin above × 2 the upper limit of normal [ULN] will be not included. In addition the treatment will be stopped in the event of an increase of hepatobiliary markers (see § 9.7).

Choice of the dose and duration of treatment

Eltrombopag dosing requirements are individualised. The objective of treatment is not to normalise platelet counts, but to obtain a platelet count necessary to reduce the risk of perioperative bleeding. In clinical studies in ImT, platelet counts generally increased within 1 to 2 weeks after starting eltrombopag and decreased within 1 to 2 weeks after discontinuation. The recommended starting dose of eltrombopag in adults and paediatric (6-17 yrs) population is 50 mg once daily. To date the tablet formulation for very young children (1-6 yrs) is not available in France. This is the reason for non-inclusion of patients below 6yrs in our study.

In the present trial, the dose chosen is the minimal dose to reach the safety level (80 G/L) within 3-4 preoperative weeks. Doses are those used in the indication of primary ImT.

- Preoperative treatment

The maximal duration of preoperative treatment is 4 weeks. Treatment is initiated at the standard starting daily dose of 50 mg for 2 weeks. As soon as the safety level of platelet count is obtained, the patient could be operated. Should this level is reached after 2 weeks, the procedure could be performed but if it is not the case or if the scheduled date of procedure cannot be anticipated for practical reasons, eltrombopag treatment is going on for a maximum of 2 more weeks, at the same daily dose of 50 mg if the platelet count is between 50 and 150 G/l, reduced to 25 mg/d if the platelet count is ≥150 G/l, stopped if the platelet count is ≥ 200 G/L or increased to 75 mg if the platelet count is ≤50 G/l.

Therefore, the maximum authorized daily dose is 75 mg/d and the minimum maximum total doses administered during the 4 weeks preoperative weeks may vary between 700 and 1750 mg.

- Postoperative treatment

Following discontinuation of eltrombopag, platelet counts return to baseline levels within 2 weeks in the majority of patients. For procedures performed without preoperative or rescue PC transfusion but requiring that the safety level of platelets be sustained for longer time in order to prevent delayed bleeding, eltrombopag treatment can be prolonged for a maximum of 1 week at a dose adjusted on platelet counts according to the same algorithm as above. A decrease of dose is expected due to the inflammatory state in the postoperative period.

6.2. MEDICINAL PRODUCT CIRCUIT

6.2.1. SUPPLY OF PRODUCTS

Eltrombopag will be supplied free for the study by NOVARTIS Pharma SAS (Appendix II)

The 50 mg and 25 mg eltrombopag tablets will be ordered by the coordinating pharmacy at Toulouse Hospital, which has contacts with the laboratory concerned:

Novartis Pharma SAS
8 / 10 Henri Sainte Claire Deville
CS 40150
92563 RUEIL MALMAISON CEDEX
Tél : 33-155476000

6.2.2. MEDICINAL PRODUCT PACKAGING

For this study, we will use the 50 mg and 25 mg eltrombopag tablets in their original packaging, provided by Novartis Pharma SAS.

6.2.3. MEDICINAL PRODUCT LABELLING

Eltrombopag will be labelled by the coordinating pharmacy, in accordance with regulations. The labels will contain the following information:

- The name and address of the sponsor
- The study references
- A free field for the patient's initials and randomisation number
- The dosage
- The batch number
- The expiry date
- The route of administration
- Essential information for product storage
- The following statements: "Use under strict medical supervision", "Drug for clinical trial"
- Precautionary information

6.2.4. DISTRIBUTION AND MANAGEMENT OF MEDICINAL PRODUCTS

The study treatments will be distributed to all pharmacies study sites by the coordinating pharmacy at Toulouse Hospital, under pharmacist responsibility.The delivery will be performed when the patient's inclusion is confirmed to the coordinating investigator. .

The treatment will be provided in 2 delivery as the dose may change after the two first weeks.

On the first visit Eltrompobag will be given for two weeks at 50mg/d dose.

On the second visit the Eltrompobag will be given for two weeks at 25, 50mg/d or 75mg/d. the dose will be clearly noted on the prescription form, depending of the patient's platelet count after the first two weeks of therapeutic.

The study treatments will be dispensed by the investigating site dispensaries' pharmacists (PUIs, for "pharmacies à usage intérieur") on presentation of the study prescription completed by a declared investigating physician. Drugs will be dispensed at Inclusion (V1) and Pre-procedural (V2) visits. Each dispensation will be reported on an accounting form for each patient.

6.2.5. STORAGE

The study treatments must be stored away from light and humidity, at room temperature.

6.2.6. RETURN AND DESTRUCTION OF UNUSED PRODUCTS

Empty and unused drug packages will be sent back to the investigating site's PUIs. For each return, the pharmacist of the investigating centre will complete an accounting form, with the date of return and the number of remaining tablets.

Permission for the destruction of returned or unused treatments will be given by the study clinical research assistant (CRA), delegated by the sponsor. The destruction of treatments will be recorded on a certificate of destruction given by the coordinating pharmacy.

7. ASSOCIATED TREATMENTS AND PROCEDURES

It is necessary to refer to the RCP of Revolade for the consideration of drug interactions.

7.1. APPROVED ASSOCIATED TREATMENTS/PROCEDURES

Usual treatments required in post-operative period, including antifibrinolytics (tranexamic acid) if indicated and medical prophylaxis of postoperative venous thromboembolism (low molecular weight heparin).

7.2. PROHIBITED ASSOCIATED TREATMENTS/PROCEDURES

Avoid anti-platelets and non-steroidal anti-inflammatory agents unless formally required for patient's condition.

8. JUDGEMENT CRITERIA

8.1. MAIN JUDGEMENT CRITERION

The main judgment criterion (primary endpoint) will be the performance of the invasive procedure in safe conditions without requirement of PC. This defines the "successful procedure", and encompasses:

- an increase in platelet count ≥80 G/L (safety level) before the procedure,
- and a procedure performed without transfusion of PC at any time during the study period.

The details of the invasive act will be left to the discretion of the operator to ensure that the results of the study can be generalized to as wide a group of patients as possible.

8.2. SECONDARY JUDGEMENT CRITERIA

- Number, percentage, severity and type of adverse events during the treatment and the 30 days following the intake of the last tablet.
- Number and percentage of patients with excessive bleeding in spite of a platelet count above the safety level. Bleeding will be clinically evaluated by the local medical/surgical team. A rating system for evaluation of effective hemostasis (excellent, good, poor) will be provided in the case report form. Any excessive bleeding or complication due to bleeding, or postoperative thrombosis will be qualified as serious adverse event and reviewed by an independent safety board (Event validation committee §12). Depending on the type of invasive act, relevant items for excessive bleeding may be: increased duration of surgery due to bleeding, reoperation for bleeding, blood loss estimated from blood-stained dressings or cumulative volume collected in suction drains, hemoglobin drop, requirement of red blood cell transfusion, prolongation of hospital stay, systematic imaging for hematoma after a biopsy of an internal organ, (non-exhaustive list, see ref 14).
- Number and percentage of patients with vascular thrombosis. Symptomatic thrombosis will be diagnosed by appropriate objective methods and reviewed by an independent safety board.

- Doses of eltrombopag and duration of treatment required to obtain the predefined safety levels. A poor response is defined by a platelet count remaining below the safety levels of 80 G/L, whether or not eltrombopag was taken (i.e. including discontinuation of treatment for safety reasons).
- Kinetics of platelet recovery under treatment and after discontinuation.
- Change in platelet size among patients with macro- or micro-thrombocytopenia.
- Value of baseline serum thrombopoietin and baseline platelet level to predict response to the drug.

9. STUDY PROCEDURE

9.1. STUDY CALENDAR

- Start of inclusions: after favourable advices of regulatory agencies, ethic committee ANSM and CNIL
- Duration of the inclusion period: 48 months, or less if the planned number of patients has been reached.
- Duration of each patient's participation: 7 to 9 weeks
- Total duration of the study:54 months

9.2. TABLE SUMMARISING THE TYPICAL PATIENT FOLLOW-UP

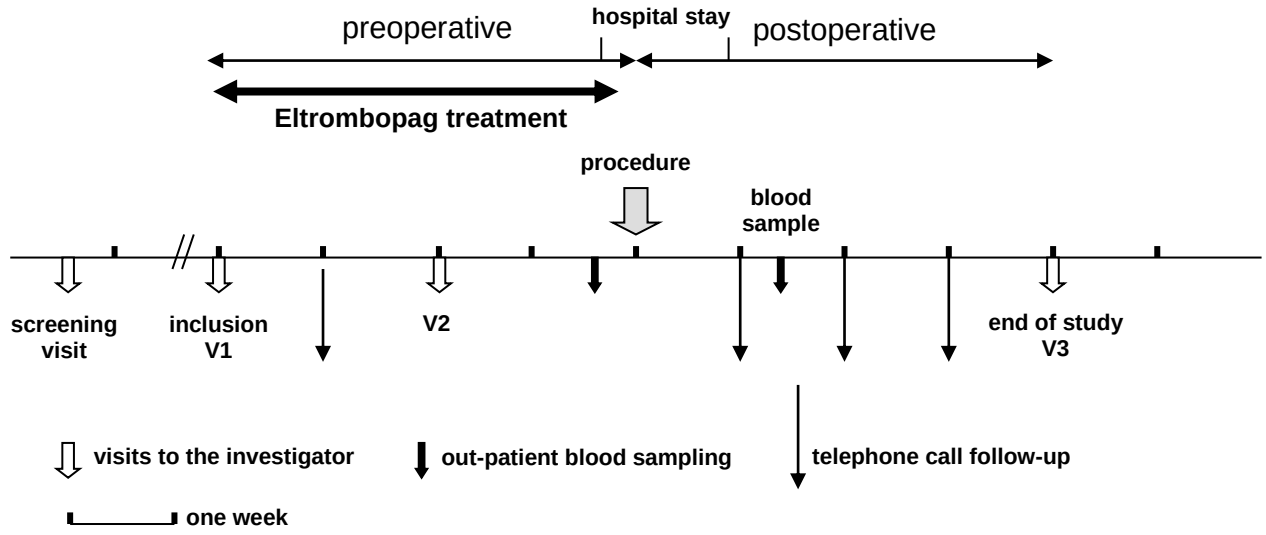
week	screening >- 4	V1 Inclusion -4***	TC1 -3	V2 -2	TC2 -1	*	Procedure 0	TC3 +1	* +1	TC4 +2	TC5 +3	V3 End of study +4
Informed consent	✓											
Clinical exam (standard care)		✓		✓			✓					
Biological exam. (standard care)	✓	✓				✓	✓		✓			
clinical and biological exam. specific to trial		✓		✓								✓
telephone call (TC)			✓		✓			✓		✓	✓	
eltrombopag treatment		start	on	on	on	on	off**					
Adverse event collection		✓	✓	✓	✓		✓	✓	✓	✓	✓	✓

* biological control performed outside the investigator centre 48 h before the procedure and 1 week after the procedure.
** For a majority of patients, the treatment is discontinued on the eve of the procedure. For procedures requiring a prolonged period of haemostasis, eltrombopag treatment at adjusted dose may be prescribed up to 6 additional days in the post-procedure period. In that case, the follow-up will be prolonged till 4 weeks after the last drug administration (see §9.5).
*** The typical scheduled delay between V1 and the procedure is 4 weeks which is the maximal duration of preoperative treatment. Treatment is initiated at the standard starting daily dose of 50 mg for 2 weeks; Then, after the dose is adjusted to platelet counts. If the safety level of platelet count is obtained at V2, the patient could be operated and the treatment is maintained at the adjusted dose until the procedure. If it is not the

case or if the scheduled date of procedure cannot be anticipated for practical reasons (see §6.1), the treatment will be given at adjusted dose for a maximal duration of 4 weeks.

In addition to the visits, the patient will be follow-up by weekly telephone call and blood sampling for monitoring platelet count and hepatobiliary markers in the preoperative period 2 weeks after starting the treatment, within 48h before the procedure and in the postoperative period, one week after the procedure or until return of platelet count or hepatobiliary markers to baseline levels.

A typical chart of follow-up, which may vary according to the type of invasive procedure, duration of treatment and of the in-hospital period, is shown below:



9.3. SCREENING VISIT

The screening visit is conducted by the investigating doctor. The screening visit occurs several weeks and, at the latest, a few days before the inclusion visit. It usually corresponds to a consultation in the specialised centre for haemorrhagic diseases where the patient is followed, once an invasive procedure at significant bleeding risk is planned (standard care). The aim of this visit is to establish the perioperative management of the patient in coordination with the medical/surgical team who will perform the procedure. During this visit, if the type of thrombocytopenia and the nature of the procedure suit the inclusion criteria (formal advice of steering committee required), the patient can be considered as eligible for participating to the trial.

During the screening visit, the investigating doctor provides the patient with research information on study protocol and answers all his or her questions about the objective, the nature of constraints, foreseeable risks and benefits expected from the study. He also explains the patient's rights in relation to a biomedical research study and checks his eligibility criteria. A copy of the Patient Information and Informed Consent form are then given to the patient by the investigating doctor.

After this information meeting, the patient has a period of time to consider his decision. The investigating doctor is responsible for obtaining the patient's written informed consent. If the patient agrees to participate, he (she) and the investigator clearly write their names and first names, date and sign the

consent form. As soon as the signed informed consent form has been received, the inclusion visit (V1) is planned.

The various copies of the Patient Information and Informed Consent form are then distributed as follows:

- A copy of the Patient Information and signed Informed Consent form is given to the patient.
- The original copy is kept by the investigating doctor (even if the patient moves house during the period of the study) in a safe place inaccessible to third parties.

The above procedure applies to the paediatric population. In this case, the parents or the legal representative should receive the information and give the written informed consent and information sheet adapted to the age (6-12, or 13-17 years) are given and explained to the patient.

9.4. INCLUSION VISIT (V1)

The inclusion visit is conducted by the investigating doctor 4 weeks before the scheduled procedure. Before any examination related to the study, the investigator should have obtained the patient's (or legal representative) informed, written and freely given consent Once the consent form has been signed, the following clinical and biological examination is performed.

- general physical examination
- full blood count, including mean platelet volume determination and peripheral blood smear to exclude cellular morphologic abnormalities.
- plasma ß HCG for women at reproductive age
- standard biochemistry to exclude altered hepatic and renal function (see non-inclusion/exclusion criteria), including the measurement of serum alanine aminotransférase (ALT) and bilirubin.
- blood group determination (if unknown)
- plasma TPO (centralised lab)

If all inclusion criteria and none of the criteria for non-inclusion are fulfilled (§ 5.1 and 5.2), eltrombopag tablets (50 mg) for 2 weeks are given to the patient, with instructions for follow-up.

9.5. FOLLOW-UP (TELEPHONE CALLS AND VISITS).

➢ <u>Preoperative period</u>

At the end of the 1st week of treatment, the patient is contacted by telephone for evaluation of the tolerance and compliance to treatment. At any time, in case of unexpected symptom, the patient can contact the investigator team for advice.

At the end of the 2nd week, a visit at the investigator centre (V2) is planned, a control of platelet count, ALT/bilirubin is performed and the results are communicated without delay to the investigator for dose adjustment (§ 6.1). After confirmation of the date of procedure, dose-adjusted treatment is prescribed and eltrombopag tablets (25 or/and 50 mg) are given to the patient for the period of time till the procedure.

The rules for interrupting treatment in the preoperative period are the occurrence of a serious adverse event reaction, the choice of the patient face to a non-serious adverse event, a platelet count ≥ 200 G/L, or the elevation of ALT/bilirubin as follows: ALT ≥3 ULN and bilirubin ≥2 ULN [>35% direct bilirubin]; ALT ≥5 ULN; ≥3 ULN if associated with the appearance of hepatitis symptoms or rash. For patients with MYH9-RD: alanine aminotransferase (ALT) or bilirubin levels ≥5 ULN, or 3 times the levels measured at inclusion (2 times if associated with the appearance of hepatitis symptoms or rash).

Two days before the surgery, biological control (platelet count and volume, ALT/bilirubin) is performed. The protocol for the management of the procedure is established with the medical/surgical team:

- no administration of PC if the desired platelet safety level has been reached,
- or, conversely, treatment with preoperative administration of PC at standard dose.

For a majority of patients, the treatment is discontinued on the eve of the procedure. For procedures requiring a prolonged period of haemostasis, eltrombopag treatment at adjusted dose may be prescribed up to 6 additional days in the post-procedure period. In that case, the follow-up will be prolonged till 4 weeks after the last drug administration.

➢ Postoperative period

On the day of procedure and in the initial postoperative period (i.e. until the patient discharge), physical examination, full blood cell counts and all investigation to assess the absence of excessive bleeding (see § 8.1) are performed daily (standard care). Rescue PC transfusion can be administered if required on the judgement of the medical/surgical team.

After discharge, the patient is contacted by telephone by the investigator team once a week for evaluation of tolerance. At any time, in case of unexpected symptom, the patient can contact the investigator team and/or the medical/surgical team for advice or a visit, if needed. Full blood cell counts and control of ALT/bilirubin, are performed weekly in the lab of choice of the patient until return to baseline values.

Should eltrombopag be given for an extra-week (§ 6.1), the same follow-up applies but dose-adjustment is performed if necessary and the same rules for interrupting treatment as in the preoperative period apply.

9.6. END OF STUDY VISIT

The end of study visit is conducted by the investigator doctor and occurs 4 weeks after the last intake of eltrombopag (whether or not the study has been prematurely interrupted, see §9.7). In practice for a majority of patients, it will occur 4-5 weeks after the procedure.

During this visit, the patient has a physical examination, a biological control of blood cell count (including platelet count and volume) and standard biochemistry including ALT/bilirubin, and a standardized interview for a comprehensive assessment of the tolerance of the treatment by the patient, including a possible reduction of spontaneous bleeding during the period of increased platelet count.

9.7. RULES FOR INTERRUPTING THE STUDY

The study can be interrupted for one of the following reasons:

- withdrawal of consent to participate to the trial,
- change of plan (delay, anticipation, annulation…etc.) regarding the invasive procedure by patient's choice or medical/surgical team's choice.
- major deviation of protocol.

Interruption of treatment for the occurrence of an adverse event, clinical or biological, is not a reason for interrupting the study (it will be analysed as a failure of the strategy).

Patient interrupting the study but who have taken at least 1 tablet of eltrombopag will be followed for 4 weeks after the last intake until the end of study visit, in the same manner as patients who have completed the study.

9.8. CONSTRAINTS RELATING TO THE STUDY

- The constraints of participating to the study is the intake of a tablet once a day during the weeks before the procedure, 2 additional venous blood sampling before and 3 after (about 45 ml of blood for the whole study) for determination of the kinetics of the platelet response, and 3 extra-visits (inclusion, mid-term of preoperative period and end of study) at the investigator's centre.
- The patient cannot participate to another study between the inclusion and the end of study visits.
- The patient will be not remunerated for his(her) participation to the study.
- All travel costs specific to the study will be supported by the promoter.

9.9. COLLECTION OF PHYSIOLOGICAL SAMPLES

There will be no collection of biological samples .Serums for the determination of endogenous TPO sampled at the inclusion visit will be stored frozen locally, send to a central laboratory and destroyed at the end of the study.

10. MANAGEMENT OF ADVERSE EVENTS AND NEW FACTS

10.1. DEFINITIONS

Adverse event (article R.1123-46 of the French Public Health Act)

Any harmful event occurring in a person taking part in a biomedical research study, whether or not that event is linked to the study or to the product being investigated in the study.

Adverse reaction (article R1123-46 of the French Public Health Act)

All untoward and unintended responses to an investigational medicinal product related to any dose administered

Serious adverse event (article R.1123-46 of the Public Health Act and the ICH E2B guide)

Any undesirable event which:

- ✓ leads to death,
- ✓ endangers the life of the person taking part in the research study,
- ✓ necessitates admission to hospital, or prolongation of hospitalisation,
- ✓ causes serious or sustained incapacity or handicap,
- ✓ is expressed by a congenital anomaly or malformation,

- ✓ or any event considered to be medically serious,

and concerning the drug, whatever the dose administered.

Unexpected adverse event (article R.1123-46 of the French Public Health Act)

Any adverse effect of the medicinal product, the nature, severity, frequency or evolution of which does not conform to the information given in the files submitted to the ethics committee for approval or to the relevant authority in application for marketing authorisation.

For the purposes of this study, a SAE is considered "unexpected" when it varies in nature, intensity, frequency or outcome from information provided in the current Investigator's Brochure of eltrombopag.

New fact (article R1123-46 of the French Public Health Act)

New safety information which could lead to re-evaluation of the benefit/risk ratio of the study, or which may be sufficient to envisage modifications to documents concerning the study, to the way the study is conducted, or, if necessary, to the way the product is used.

10.2. DESCRIPTION OF EXPECTED SERIOUS ADVERSE EVENTS

The 2 serious adverse events (SAE) expected in the context of this study are the risk of perioperative bleeding and the risk of vascular thrombosis.

- ➢ <u>Perioperative bleeding</u>

By definition, the invasive procedures selected as inclusion criteria in this study are at mild or high risk of bleeding in subjects with normal haemostasis. A platelet defect in number (thrombocytopenia) or in function (thrombopathy) increases the risk. It is the reason why prophylactic PC transfusion is currently mandatory to reach a safety level adapted to the procedure. Recovery of endogenous platelets induced by a TPO mimetic to the same level could be an alternative to PC.

Even in patients with normal haemostasis, or thrombocytopenic patients appropriately transfused with PC before the procedure, bleeding may occur for various reasons, requiring red blood cell transfusion in some instances (e.g. major orthopaedic surgery). In the present study, if the safety level of platelet count is obtained after eltrombopag, the possibility that endogenous platelets may be not fully functional should be considered. Of note, in the above mentioned studies of patients with MYH9-type treated with eltrombopag (8, 9), spontaneous bleeding diathesis quickly improved in all symptomatic patients responder to the drug and interestingly, the clinical benefit lasted for more than 2 weeks after treatment discontinuation. So at least in this type of IT, there is a parallelism between platelet count and haemostatic function.

However, as no simple laboratory test is currently available to exclude a mild platelet functional defect, in case of excessive bleeding evaluated by the medical/surgical team, without evidence of surgical or other medical reasons, rescue PC transfusions will be performed without delay.

- ➢ <u>Vascular thrombosis</u>

The occurrence of a venous thromboembolic event in the postoperative period for surgeries which expose to this complication (e.g. abdominal, gynaecologic, urologic, cancer and orthopaedic) is a concern in

the general population. This risk is largely prevented by physical measures and the administration of prophylactic anticoagulants (usually low molecular weight heparins), but these measures are not 100% efficient (for example, the rate of symptomatic deep venous thrombosis in major orthopaedic surgery under well performed medical prophylaxis is between 0.5 and 1.2 % in recent studies.

In long term treatment of ImT (21), thrombotic events are reported to be "uncommon" (≥ 1/1,000 to < 1/100). The largest experience in surgical context is an observational study of 31 patients who underwent treatment with a TPO mimetic (romiplostin or eltrombopag) before splenectomy (32). Two patients developed a thrombosis (one asymptomatic portal thrombosis and one symptomatic non-fatal pulmonary embolism), 30 days and 6 days after the cessation of treatment respectively. In patients with chronic liver disease and thrombocytopenia undergoing various elective invasive procedures, treatment with eltrombopag was associated with an increased incidence of portal thrombosis as compared with placebo (33).

To take into account this serious event, potentially related both to the medicinal product and to the procedure, we implemented the protocol with the following measures:

- Patients with personal history of venous or arterial thrombosis, known familial thrombophilia, chronic hepatitis or cirrhosis with moderate to severe liver failure, will be not included;
- the dose of eltrombopag will be adjusted to avoid unnecessary high platelet counts above 150 G/L;
- an active prophylaxis of postoperative venous thromboembolism (physical measures and low molecular weight heparin) in surgeries at risk for this complication will be mandatory.

Besides notification of a serious adverse event to the Pharmacovigilance Unit and to NOVARTIS, the case will be reviewed by an independent event validation committee (see § 12) for deep analysis of the cases and event validation.

Any serious adverse reaction reported in this study will be considered as "unexpected" (SUSAR) if it is not listed in section 10.2 of the protocol or in Investigator's Brochures of eltrombopag.

10.3. ACTION TO BE TAKEN IN THE CASE OF AN ADVERSE EVENT OR NEW FACT

*** Adverse events collection**

Participating investigators will assess the occurrence of AEs and SAEs at all participant evaluation time points during the study.

All AEs and SAEs whether reported by the participant, discovered during questioning, directly observed, or detected by physical examination, laboratory test or other means, will be recorded in the participant's medical record and on the appropriate study-specific case report forms. All AEs must be recorded in the participant's medical record, stating the duration of the event, action taken by the investigator and outcome of the event. The investigator must evaluate the causal relationship between the study drug and the AE.

*** Serious adverse events notification**

The investigator must immediately notify the sponsor on the day that he becomes aware of it of any serious adverse event or any new fact, if it occurs:

- after the date of signature of the consent form,
- at any time during the period of follow-up planned by the study for the participant,

TYPE OF EVENT	NOTIFICATION METHOD	TIME LIMIT FOR NOTIFYING THE SPONSOR
Non-serious AE	In the case report form	No immediate notification
SAE	Initial SAE declaration form + written report if necessary	**Sponsor to be notified immediately**
New fact	Declaration form + written report if necessary	**Sponsor to be notified immediately**
Pregnancy	Pregnancy declaration form	On confirmation of the pregnancy

Name of sponsor/Vigilance unit :
University hospital of Toulouse/Dr Pascale Olivier-Abbal
Email : vigilance.essaiscliniques@chu-toulouse.fr
Fax No : +33 (02)5 61 77 84 11

All these events must be monitored until they are completely resolved. The investigator will send the sponsor additional information (additional declaration form) concerning the evolution of the event not mentioned in the initial report. Pregnancy occurring during the period or immediately after a study does not constitute an SAE. However, a pregnancy must be notified in the same way as an SAE because it requires particular monitoring throughout its duration. Any anomaly observed in the foetus or child will then be notified. Any elective termination of pregnancy (ETP), medical termination of pregnancy (MTP) or spontaneous abortion must give rise to a notification of pregnancy, and if it necessitated hospitalisation, it must be passed on in the same manner as an SAE.

10.4. DECLARATION AND RECORDING OF UNEXPECTED SERIOUS ADVERSE REACTIONS AND NEW FACTS

The sponsor/vigilance unit immediately declares any suspected unexpected serious adverse reaction (SUSAR) and new facts occurring during the study:

- to ANSM [the French Agency for the Safety of Health Products],
- to the relevant ethics committee. If necessary, the committee ensures that subjects participating in the study are informed of the undesirable effects and that they confirm their consent.

In addition, the sponsor/vigilance unit will record all the SUSARs in the EudraVigilance database.
SAEs, expected SAEs and SUSARs will be notified on yearly basis by the sponsor in an annual safety report (or Development Safety Update Report – DSUR), within 2 months following 1rst authorization anniversary date.

11. STATISTICS

11.1. CALCULATING THE SIZE OF THE STUDY

- Primary endpoint and outcome measures

This is an open cohort study without comparator. The main judgement criterion is the performance of an invasive procedure at risk of bleeding in safe condition without requirement of PC administration (prophylactic before the procedure or rescue of bleeding per- or postoperative).

If not treated with eltrombopag, 100 % of patients included would have received at least prophylactic PC. So the measured variable is qualitative (success: no PC, failure: administration of PC) and the result will be expressed in % rate of success, that may vary from 0 to 100%.

- Working hypothesis

To date, we are aware of only 16case reports of an elective surgery performed in 9 patients with severe IT after treatment with a TPO mimetic (3 eltrombopag, 1 romiplostim)(24-28). Most of them were successful, without requirement of PC transfusion. Although we cannot exclude a publication bias, this reasonably suggests a relatively high rate of success. On the other hand, in a small group of 12 patients with MYH9-type IT, a major response in platelet count, close to the safety level for most of invasive procedures, was obtained in 8 patients using the same dose of eltrombopag and in the delay as proposed in our study (8). Partial or complete platelet response was observed without major saefety concern in a group of 24 patients with various IT similarly treated with eltrombopag (9).

Accordingly, we make the following hypothesis. Reaching a proportion of success of 60 % or more without major safety concern would deserve recommendation for use and set up a registry to increase our knowledge on this new option. A proportion of 20% or less would deserve recommendation against use. Intermediate results would deserve further investigation in subpopulations of ITs.

- Feasibility

A sample size of 25 invasive procedures was determined by the feasibility of recruitment (rare disease, relatively rare condition, see §5.3). Due to the heterogeneity of ITs, this number 25 appears to be both necessary and sufficient. The population of patients with one of candidate IT is around 300 in France. This number may be underestimated since these patients, as usual in rare diseases, may remain not diagnosed if they have no spontaneous severe bleeding symptoms.

The widespread MHEMO network recently approved by the DGOS provides a unique opportunity to set up such a study with 25 participating centres, all having an excellent experience in the management of haemorrhagic diathesis. We estimate 1-3 patients eligible per centre. Due to the exclusion criteria and the constraints of a clinical trial, the inclusion rate is estimated to be 1:2 and the chance for each centre to include during the trial period is between 0 and 2 case(s). A number of 25 patients is therefore realist, if not conservative, for a period of 30 months.

Finally, significant loss of follow-up is unlikely. The study is relatively short for each patient (7-9 weeks) and is performed in a context where the supervision of a physician experienced in the treatment of haematological diseases is usually asked by the patient itself.

- In conclusion, a number of 25 patients enrolled is realist. This sample size is in accordance with the number of patients usually included in early phase II trials (small number of diseased patients) and in pilot studies (34) The 95% confidence interval of the success rate (percentage of patients who will not

require PC transfusion) provided by this sample will be rather large (± 19% for and estimated success rate of 60%). The question whether or not eltrombopag avoids platelet transfusion, in conditions where it would have been otherwise performed, is likely to be answered with an experience in 25 surgical procedures. As an example, the note for guidance of CPMP (European Medical Agency) to assess the efficacy and safety of plasma-derived products for the treatment of hemophiliacs requires a minimum of 10 different surgical procedures in 5 patients. However, we acknowledge that the study is exploratory, aimed at providing a first estimation of this success rate and will have to be followed by a registry continuously monitoring IT patients treated with eltrombopag in this context.

11.2. STATISTICAL METHODS USED

The analysis plan will have to be validated by the steering committee of the study.

The sample of patients included in this study will first be described using usual descriptive statistics: number and percentage for categorical variables; median, interquartile range, and extreme values for continuous variables and if the distribution does not depart from normality, mean and standard deviation.

The primary endpoint (success rate after eltrombopag administration) will be the percentage of patients who will not require PC transfusion before, during, or after the invasive procedure. A 95% confidence interval will be provided.

Secondary categorical endpoints (percentages of patients experiencing bleeding, vascular thrombosis, and adverse events will also be assessed with a 95% confidence interval. Adverse events will also be described according to the type and the severity of the event. The distribution of secondary continuous endpoints will be described by providing the following indicators: median, interquartile range, extreme values. The normality of the distribution will be graphically studied. If the distribution is in accordance with a normal distribution, mean and standard deviation will also be provided. The kinetics of platelet recovery will be described for each patient by graphically drawing platelet count according to time. Changes in laboratory parameters after eltrombopag administration will be assessed by comparing the mean of continuous biological parameters before eltrombopag administration to the mean after administration. A paired T-test will be used given that the difference of the means is normally distributed. In case of distribution departing from normality a paired ranked test will be used. Level of significance will be set at 0.05. The potential predictive value of baseline serum thrombopoietin level to predict platelet response will be first studied by comparing mean level of thrombopoietin in patients with a successful eltrombopag administration (no requirement of PC transfusion) to those with a failure (t-test or Kruskal-Wallis test according to the distribution of the baseline thrombopoeitin level). Then a modelisation based on a logistic regression model with success / failure of eltrombopag administration as dependent variable, will be explanatorily proposed with one or two main adjustment variables such as age, or gender. The same analysis will be performed with baseline platelet count as variable potentially predictive of platelet response to eltrombopag.

12. MONITORING THE STUDY

The monitoring of the study will be performed on each site by a Coordinator of Clinical Study, assisted by a Clinical Research Technician and a Clinical Research Assistant, recruited by the University Hospital of Toulouse (see the financial form).

- Steering committee

A steering committee of 8 co-investigators involved in the conception of the study is constituted as follows:

- Pr MC Alessi, National Coordinator of the CRTC, (University Hospital, Marseille)
- Dr M Fiore (CRTC; University Hospital, Bordeaux)
- Dr MF Hurtaud (CRTC, University Hospital Paris-R Debré)
- Dr E Demaistre (University hospital Dijon)
- Dr R Favier (CRTC, University Hospital Paris-Trousseau)
- Dr V Proulle (CRTC, University Hospital Paris-Bicetre)
- Pr S Blanche (Centre de Référence des Déficits Immunitaires Héréditaires, University Hospital Paris-Necker)
- Dr T Leblanc (Haematology, University Hospital Paris-R Debré)
- Pr P Sié, coordinating investigator, (CRTC, University Hospital, Toulouse)
- and the Coordinator of Clinical study mentioned above.

Besides regular web exchange and information on the progress of the study, the committee will meet at the annual meetings of the CRTC, or of the MHEMO network.

The role of steering committee is to validate the cases, to communicate on the advancement of the study to the co-investigators and abroad (manufacturer, patient association), to discuss all new data relative to the project, including DSMB recommendations, potential amendments, to prepare the final report and publications.

- Event Adjudication Committee (EAC)

All safety data (AE and SAE) will be investigated by the Clinical research study vigilance unit of the promotor.

In addition an independent EAC, composed as follows, will adjudicate all unusual bleeding and all thrombotic events:

- Pr CM Samama, Anaesthesiologist (University Hospital, Paris-Cochin)
- Pr T Lecompte, Haematologist, (University Hospital Genève Switzerland)
- Pr G Pernod, Vascular Medicine (University Hospital, Grenoble)

- Data Safety Monitoring Board (DSMB)

An independent DSMB (one methodologist, one anesthesiologist and one vigilance unit manager, with experience in clinical trials) will review safety data and will make recommendations regarding potential

problems at any time. This board will provide the Steering committee and the Sponsor with advice on the continuation (with modification of the trial protocol if necessary), arrest or interruption of the ELPOT trial.
The DSMB will review safety data after the enrollment of the first 5 patients and after the enrollment of 20 patients who experienced the surgical procedure. Apart from these dates, the DSMB will meet *ad hoc* at the request of the Steering committee or the Sponsor, in case of serious safety issue.
DSMB composition, role and missions are described in a separate Charter.

13. RIGHT OF ACCESS TO DATA AND SOURCE DOCUMENTS

13.1. ACCESS TO DATA

The sponsor is responsible for obtaining the agreement of all the parties involved in the study in order to guarantee direct access in all the sites where the study is being conducted to source data, source documents and reports, so that he can control their quality and audit them.

The investigators will make available to the people with a right of access to these documents under the legislative and regulatory provisions in force (articles L.1121-3 and R.5121-13 of the French Public Health Act) the documents and individual data strictly necessary for monitoring, carrying out quality control and auditing the biomedical research.

13.2. SOURCE DATA

The source documents are the medical records of visits, hospital stay and surgery and biological results, during the entire period of the participation of the patient to the study (or until resolution of an adverse event, if occurred).

13.3. CONFIDENTIALITY OF DATA

In accordance with the legislative provisions in force (articles L.1121-3 and R.5121-13 of the French Public Health Code), people with direct access to source data will take all necessary precautions to ensure the confidentiality of information relating to investigational drugs, research studies and people taking part in them, particularly as regards their identity and the results obtained. These people, like the investigators themselves, are subject to professional secrecy.

During the biomedical research study or when it is over, the information collected on the people taking part in it and forwarded to the sponsor by the investigators (or any other specialist personnel involved) will be made anonymous. Under no circumstances may the uncoded names or addresses of the people concerned appear in it.

The data will be made anonymous by using a code with the number of the site of inclusion (1 to 26), the 1st letters of the name and surname of the patient, and the order of inclusion in the site (e.g. 12FB02).
The list of inclusion codes with corresponding patient identities will be locked with regularly updated passwords, and stored in a computer with restricted access. It will be different from the data files used for research analysis, which will only mention the code number of the observation.

The sponsor will ensure that each person taking part in the study has given his agreement in writing for access to the individual data concerning him which is strictly necessary for quality control of the study.

14. QUALITY CONTROL AND ASSURANCE

14.1. INSTRUCTIONS FOR COLLECTING DATA

All the information required by the protocol will be entered in a paper case report form and an explanation will be provided for each piece of information which is missing. The data will be collected as and when they are obtained, and transcribed into these forms in a clear and legible manner.
Incorrect data noted in the case report forms will be clearly crossed out and the new data copied in beside the crossed-out information, with the initials, date and possibly a reason, by the investigator or authorised person who has made the correction.

14.2. MONITORING THE STUDY

The study will be monitored by a clinical research technician. He will be responsible to the coordinating investigator for:

- the logistics of and monitoring the study,
- producing reports concerning its state of progress,
- verifying that the case report forms are updated (request for additional information, corrections, etc.),
- sending samples,
- transmitting SAEs to the sponsor.

He will work in accordance with the standard operating procedures, in cooperation with the clinical research assistant appointed by the sponsor.

14.3. QUALITY CONTROL

A clinical research assistant appointed by the sponsor will regularly visit each study centre during the process of setting up the study, one or more times during the study depending on the frequency of inclusions, and at the end of the study. During these visits, the following aspects will be reviewed:

- informed consent,
- compliance with the study protocol and the procedures set out in it,
- the quality of the data collected in the case report form: its accuracy, missing data, consistency of the data with the source documents (medical records, appointment diaries, the originals of laboratory results etc.),
- management of medicinal products if appropriate.

Each visit will be recorded in a written monitoring report.

14.4. DATA MANAGEMENT

Data will be entered in simple by the technician research assistant in the paper case form and validated by the investigator of each site in accordance with the data management plan defined jointly by the coordinating investigator and the Methodology and Data Management Centre (methodologist, data manager and statistician). The complete form will be back to the data analysis centre (University Hopital Toulouse) soon after completion of each case report. Data analysis will be performed independently from the drug manufacturer (NOVARTIS).

14.5. AUDIT AND INSPECTION

An audit may be performed at any time by people appointed by the sponsor who are independent of those responsible for the study. The aim of an audit is to ensure the good quality of the study, that its results are valid and that the law and regulations in force are being observed.

The investigators agree to comply with the requirements of the sponsor and the relevant authority for an audit or an inspection of the study. The audit can apply to all stages of the study, from development of the protocol to publication of the results and filing the data used or produced in the study.

15. ETHICAL AND REGULATORY CONSIDERATIONS

The sponsor and the investigator or investigators undertake to conduct this study in compliance with French law n° 2004-806 of 9th August 2004 and following Good Clinical Practice (I.C.H. version 4 of 1st May 1996 and the decision of 24th November 2006) and the Helsinki Declaration (Ethical Principles for Medical Research involving Human Subjects, Tokyo 2004).

The study is being conducted in accordance with this protocol. With the exclusion of emergency situations necessitating taking specific therapeutic actions, the investigator or investigators undertake to observe the protocol in all respects, in particular as regards obtaining consent and the notification and follow-up of serious adverse events.

This study will be submitted for approval to the ethics committee of *Sud-Ouest et Outre-Mer IV* on *3rd may 2018* for authorization to the ANSM on *30th January 2018.*

The University hospital of Toulouse, the sponsor of this study, has taken out an insurance policy covering third party liability with Gerling Company, complying with the provisions of article L1121-10 of the French Public Health Act.

The data recorded in this study will be subject to computer processing by University Hospital Toulouse in compliance with the Regulation 2016/679 of the European Parliament and of the council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation) and the French Law “Informatique et Libertés” n°78-17 of 6th January 1978 amended..

This research falls within the framework of the French "Reference methodology" (MR-001) in application of the provisions of article 54 paragraph 5 of the modified law of 6th January 1978 relating to

information, files and civil liberties. This change has been approved by the decision of 5th January 2006. The University Hospital Toulouse signed a commitment to comply with this "Reference methodology".

This research will be registered in the European EudraCT database under n° 2017-004489-88 in accordance with art. L1121.15 of the French Public Health Act.

This research will be registered on the web site http://clinicaltrials.gov/ under the n° NCT03638817

AMENDMENTS TO THE PROTOCOL

Any substantial modification, i.e. any modification of a nature likely to have a significant impact on the safety of the people involved, the conditions of validity and the results of the study, on the quality and safety of the investigational medicinal products, on interpretation of the scientific documents which provide support for the study or the methods for conducting it, is the subject of a written amendment prepared by the steering committee to be submitted to the sponsor. Prior to implementing it, the latter must obtain approval from the ethics committee and authorisation from ANSM.

Non-substantial modifications, i.e. those not having a significant impact on any aspect of the study whatsoever, are communicated to the ethics committee for information purposes.

Any amendments to the protocol must be made known to all the investigators participating in the study. The investigators undertake to comply with the contents.

Any amendment modifying the management of patients or the benefits, risks or constraints of the study is the subject of a new Patient Information and Informed Consent form which must be completed and collected according to the same procedure as used for the previous one.

16. STORAGE OF DOCUMENTS AND DATA CONCERNING THE STUDY

The following documents relating to this study are archived in accordance with Good Clinical Practice by the investigating doctors and the sponsor:

- for a period of 15 years following the end of the study

- the protocol and any amendments to the protocol
- the case record forms
- the source files of participants who signed a consent form
- all other documents and letters relating to the study
- the original copies of informed consent forms signed by participants (by investigating doctors)

The sponsor is responsible for all these documents for the regulation period of archiving. No removal or destruction may be carried out without the sponsor's agreement. At the end of the regulation archiving period, the sponsor will be consulted regarding destruction. All the data, all the documents and reports could be subject to audit or inspection.

17. RULES RELATING TO PUBLICATION

17.1. SCIENTIFIC COMMUNICATIONS

Analysis of the data provided by the study centres is performed by Methodological and Data Management Unit of the University Hospital of Toulouse. This analysis results in a written report transmitted to the ethic committee and the relevant authority.

Any written or oral communication of the results of the study must have been previously agreed by the steering committee and, if necessary, by any committee constituted for the study.

Publication of the main results will mention the name of the sponsor, all the investigators who recruited or monitored patients in the study, the methodologists, biostatisticians and data managers who took part in the study, the members of the committees set up for the study and the participation of NOVARTIS for providing the test drug. The international rules for writing and publication (Vancouver Agreement, February 2006) will be considered.

17.2. COMMUNICATION OF THE RESULTS TO PATIENTS

In accordance with the law n° 2002-303 of 4th March 2002, patients will be informed, at their request, of the overall results of the study.

17.3. CEDING DATA

The collection and management of data will be carried out by University Hospital of Toulouse. The conditions for ceding all or part of the database of the study will be decided by the sponsor of the study and will be the subject of a written contract.

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APPENDIX II: CONFIRMATION OF NOVARTIS FOR PROVIDING ELTROMBOPAG

A l'attention du CHU de Toulouse en tant que promoteur et du
Pr Pierre Sié, Responsable Scientifique de l'étude

Objet : votre demande au sujet de l'étude interventionnelle « Evaluation de l'eltrombopag en periopératoire lors de chirurgies et actes invasifs programmés chez les patients ayant une thrombopénie constitutionnelle (ELPOT) ».

Le mercredi 20 juillet 2016

Cher Pr Sié

Faisant suite à votre demande du 18 février 2016 et à nos différents échanges à ce sujet, nous avons le plaisir de vous informer que Novartis Pharma SAS est intéressée de participer au financement du projet avec mise à disposition à titre gracieux du produit eltrombopag (quantité à determiner pour 25 patients en fonction de la durée totale estimée de traitement) dont le CHU de Toulouse est le promoteur.
Ce soutien de principe reste subordonné aux conditions suivantes, qui en constituent le pré requis déterminant, leur absence de réalisation ne permettant donc pas de considérer Novartis Pharma SAS comme engagée :

- obtention de l'avis favorable du CPP et de l'autorisation de l'autorité compétente pour la réalisation de la recherche (ANSM);

- fourniture préalable :

  - de l'attestation d'assurance couvrant les risques liés à l'essai, distincte de la couverture professionnelle du promoteur, garantissant la responsabilité civile de ce dernier et celle des intervenants dans la recherche,
  - du protocole final de l'étude.

- signature préalable d'un contrat entre le CHU de Toulouse *(nom du promoteur)* et Novartis Pharma SAS. Nous vous adresserons une proposition à cet égard. Ce contrat devra notamment définir les modalités de livraison du produit, les requis en matière de pharmacovigilance, ainsi que les obligations réciproques des parties.

Vous souhaitant bonne réception de la présente, nous vous prions de croire, Cher Pr Sié en l'assurance de nos sincères salutations.

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APPENDIX III: JUSTIFICATION DE L'ÉTUDE ELPOT CHEZ LES MINEURS

Benefice potentiel du traitement chez l'enfant.

Les agonistes du recepteur de la TPO (TPO-RA : romiplostim, eltrombopag) ont une AMM chez l'adulte et l'enfant de >1 an pour le traitement en seconde ligne du Purpura Thombopénique Idiopatique (PTI) refractaire aux traitements conventionnels (corticoïdes, Ig IV, rituximab, éventuellement splenectomie) (RCP Revolade®).

Contrairement au PTI, thrombopénie acquise dont la forme chronique refractaire de l'enfant est relativement rare (1 pour 2-6. 10^6 enfant-années), les thrombopénies constitutionnelles présentent une expression clinique dès la naissance par définition, avec un risque hémorragique provoqué lors d'actes invasifs de pratique courante chez le jeune enfant (buco-dentaires, ORL, urologiques notamment pour les actes programmés). L'administration de concentrés plaquettaires (CP), prophylactique ou de sauvetage, est la seule option actuelle. Elle expose aux mêmes risques d'effets secondaires que chez l'adulte, en particulier d'immunisation après administrations répétées, et elle souffre des mêmes limites d'acceptabilité en tant que produit sanguin.

Il existe peu de données publiées sur l'efficacité des TPO-RA dans les thrombopénies constitutionnelles. Toutefois des résultats publiés de courtes séries encouragent l'évaluation clinique de l'eltrombopag chez ces patients, enfants comme adultes. Une étude prospective réalisée chez 12 patients agés de plus de 16 ans, atteints d'une thrombopénie macocytaire de type MYH9 a montré une correction complète ou partielle de la numération plaquettaire chez 11 patients et une réduction de la tendance hémorragique spontanée chez 8, sous traitement par eltrombopag selon les modalités voisines de celles de l'essai ELPOT (Pecci, 2010). Une étude prospective ouverte vs placebo chez 8 enfants (0,5-13 ans) atteints d'une thrombopénie constitutionnelle microcytaire (WAS/XLT) a montré une élévation de la numération plaquettaire combinée à une réduction de la tendance hémorragique chez une majorité d'entre eux, sans effet d'activation plaquettaire (Gerrits 2015). Dans ces deux études, les effets indésirables rapportés au médicament ont été rares et mineurs. L'expérience publiée d'eltrombopag pour la préparation à une chirurgie de patients porteurs de thrombopénies constitutionnelles (3 cas, dont un enfant de 13 ans) a montré une efficacité complète, sans nécessité de recours à l'administration de CP (Pecci 2012 ; Favier 2013 ; Fiore 2016) et sans effet indésirable.

Données de sécurité chez l'enfant

Les résultats des essais cliniques randomisés vs placebo (avec ou sans recours aux immunomodulateurs) ont établi que sur des périodes de plusieurs semaines ou mois, ces médicaments étaient aussi efficaces et bien tolérés dans la population pédiatrique que chez l'adulte (voir Buchbinder 2017 et Ly 2017 pour des revues actualisées sur les TPO-RA chez l'enfant). Les résultats des essais randomisés d'eltrombopag (Bussel 2015, Gainger 2015) ont été confirmés dans les études observationnelles. La plus large d'entre elle (Neunert 2016, Pediatric ITP Consortium of North America - ICON) a repris les observations de 87 traitements par un TPO-RA (36 eltrombopag, 51 romiplostim). Les évènements indésirables liés au traitement ont été jugés mineurs (cf RCP Revolade®), à l'exception de l'apparition d'anticorps anti-romiplostim chez un patient de ce groupe et de 2 évènements thromboemboliques sous eltrombopag, tous deux chez des patientes de 17 ans avec facteurs de risque thromboembolique associés. Au vu de ces résultats, le recours à ces médicaments est recommandé dans la même indication de PTI chronique chez l'enfant et chez l'adulte (Grainger 2017). Du fait de l'introduction récente de ces médicaments, leur tolérance lors des traitements continus de longue durée (années) doit être confortée chez l'enfant.

Les données de sécurité d'eltrombopag chez les patients porteurs d'une thrombopénie constitutionnelle (enfants et adultes) ne peuvent être déterminées à partir des courtes séries publiées plus haut. Pour ce qui concerne le risque thrombembolique, il est important de rappeler

que le PTI est une condition suspecte de risque thrombotique paradoxal (Rodighiero 2016), majoré par les traitements, ce qui n'est pas le cas des thrombopénies constitutionnelles.

Place de la population pédiatrique dans l'essai ELPOT

L'inclusion des patients pédiatriques dans le présent essai est essentielle pour au moins deux raisons:

- Le nombre de sujets nécessaire pour l'analyse statistique des résultats ne serait pas atteint sans la contribution d'une cohorte pédiatrique, sauf à prolonger de façon innacceptable la durée de la période de recrutement. Nous avons estimé par sondage des 25 centres investigateurs avant la soumission du projet que la tranche d'âge entre 6 et 17 ans représentait à elle seule environ la moitié de la population adulte potentiellement candidate à l'inclusion à l'échelon national, et évidemment 100 % des candidats pour les centres exclusivement pédiatriques (Necker, Robert-Debré). La tranche d'âge 1-6 ans béneficierait également d'une alternative aux CP, mais la formule pédiatrique d'eltrombopag en poudre se prête mal à un essai clinique. Une formule en comprimé est en développement. Elle permettrait, si elle était disponible avant la fin de l'essai (2021), d'envisager l'extension de la limite d'âge à 1 an, après soumission d'un amendement et accord des Agences.
- Il nous apparait nécessaire d'obtenir des données pédiatriques dans le cadre d'un essai clinique dans le même temps que les données chez l'adulte, pour documenter précisement les modalités d'utilisation du médicament chez l'enfant dans le contexte périopératoire.

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