# A multicentre, randomized, open-label study of romiplostim plus dexamethasone vs dexamethasone in patients with newly diagnosed primary immune thrombocytopenia

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# 1. PROTOCOL SUMMARY

## a. Sponsor

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## b. Study Title

A multicentre, randomized, open-label study of romiplostim plus dexamethasone vs dexamethasone in patients with newly diagnosed primary immune thrombocytopenia.

## c. Protocol code

RODEX

**d. Ethics Committee**

The opinion of the Ethics Committee will be obtained in accordance with local legislation in each participating country.

**e. Investigational product**

Romiplostim and dexamethasone

**f. Phase**

Phase III

**g. Study objectives**

Primary objective:

To evaluate the superiority of romiplostim plus dexamethasone vs dexamethasone alone after 6 months (≥180 days) from treatment cessation in patients with newly diagnosed primary immune thrombocytopenia (ITP) in terms of sustained response off any ITP treatment (6mSROT-50) and without WHO grade 2 or more bleeding.

Maximum time on treatment with romiplostim will be 12 months (365 days). Then, patients will be followed up for 6 additional months (180 days) after stopping romiplostim.

Secondary objectives:

- To evaluate the superiority of romiplostim plus dexamethasone vs dexamethasone alone after 6 months (≥180 days) from treatment cessation in patients with newly diagnosed primary immune thrombocytopenia in terms of sustained response off any ITP treatment (6mSROT-30) and without WHO grade 2 or more bleeding.
- To evaluate the superiority of romiplostim plus dexamethasone vs dexamethasone alone after 12 months (≥365 days) from treatment cessation, if data available, in patients with newly diagnosed primary immune thrombocytopenia in terms of sustained response off any ITP treatment (12mSROT-30 and 12mSROT-50) and without WHO grade 2 or more bleeding.
- To evaluate the superiority of romiplostim plus dexamethasone vs dexamethasone alone in terms of complete response (CR), response (R) global response (GR) and response within the target range (TR) at 6 months (Day 180), at 12 months (Day 365) from randomisation and at End of study Visit (visit 12 months after the last dose of study treatment).We will evaluate them in the total sample but also in a subgroup that excludes patients receiving any rescue treatment. Or an additional sensitivity analysis will be conducted to exclude patients receiving rescue treatment.
- To compare the time to first response defined as the time from randomization to first response (R) in both arms. We will evaluate this in the total sample and in the absence of any rescue treatment.

- To compare the proportion of patients with early response (ER) and initial response (IR) in both arms.
- To compare the duration of platelet response assessed as: the maximum number of consecutive days with platelet response (CR, R, GR and TR) and, the total number of days along the study period with platelet response (CR, R, GR and TR) in both arms. We will evaluate them in the total sample and in the absence of any rescue treatment.
- To compare the time to loss of response (LoR) in patients who achieved response in both arms.
- To compare the proportion of patients requiring any rescue treatment along the study period in both arms.
- To evaluate and compare proportion of treatment failure and time to treatment failure.
- To evaluate the safety and tolerability of study treatments in both arms.
- To compare the difference between study arms in the mean change in patients' bleeding
- To compare the change in patients' quality of life from baseline Day 1, (the day of administration of the first dose of study medication) toMonth2 (Week 8), Month 6 (Day 180), Month 12 (Day 365) and End of study Visit (visit 12 months after the last dose of study treatment) assessed SF-36v2, FACIT-F and ITP-PAQ in both arms.
- To describe and compare healthcare resources use (HRU) and loss of productivity in both study arms.

### h. Study design

This is an open label, randomized, phase 3 study designed to compare romiplostim plus dexamethasone vs dexamethasone alone in terms of sustained response off any ITP treatment in adult subjects (≥18 years old) with newly diagnosed ITP.

According to the International Working Group assessment [1] patients will be screened for study participation. Subjects who meet eligibility criteria will be enrolled. Once eligibility is confirmed, patient will be randomized. Randomization will be stratified by center with a 1:1 allocation using random block sizes, to receive dexamethasone 40 mg daily x 4 days only in the first cycle and subcutaneous romiplostim weekly for up to 12 months (ROM + DEX arm) or dexamethasone 40 mg daily x 4 days for up to 3 cycles every 14 to 28 days (DEX arm).

The monitoring will be the same in both arms with slight differences to allow for dose adjustments of romiplostim:

- In the ROM+DEX arm, patients will be reviewed weekly for 8 weeks (56 days). After Week 8, patients will be reviewed every 2 weeks (14 days) for

8 additional weeks and then monthly until Week 52 (365 days/12 months) from randomization.

    - If romiplostim is modified, patients will be reviewed weekly until a stable dose of romiplostim is reached for at least 4 weeks (28 days). After that, patients will go on with visits every 2 weeks (14 days) for 8 weeks and then monthly until Week 52 (365 days/12 months) from randomization.

- In the DEX arm, patients will be reviewed weekly until the completion of dexamethasone cycles and for a minimum of 8 weeks (56 days). After that, every 2 weeks (14 days) for 8 additional weeks and then monthly until Week 52 (365 days/12 months) from randomization.

The following assessments will be done in these visits: platelets count, bleeding score, medication, HRU associated with the ITP or its treatment and loss of productivity

Quality of life will be evaluated at Day 1 (the day of administration of the first dose of study medication), Month 2 (week 8), Month 6 (Day 180), Month 12 (Day 365) and End of study Visit (visit 12 months after the last dose of study treatment). See Study schedule for more details.

In the ROM+DEX arm, starting romiplostim dose will be 3 mcg/kg, adjusting the following weekly doses according to platelet counts following actual label indications (see section Dosage an administration, for more detailed information). Patients will weekly receive dose increases of romiplostim in increments of 1 mcg/kg up to a maximum dose of 10mcg/kg aiming for a platelet count higher than 50 $x10^9$/L. If romiplostim dose is stable for 4 weeks and platelets are higher than $50x10^9$/L, romiplostim will be tapered in 1 mcg/kg per week to a dose of 1 mcg/kg per week. If after 4 additional weeks, platelets remain greater than 50, the Interval between 1mcg/kg romiplostim injections will increase to 14 days. If after another 4 doses, platelets remain $>50x10^9$/L, romiplostim should be discontinued. If after 4 doses of romiplostim 1 mcg/kg/14 days, platelets remain still higher than $50x10^9$/L treatment with romiplostim should be ended.

Otherwise, if platelets are lower than $50x10^9$/L, treatment with romiplostim will continue until 365 days after randomisation.

If platelets are between 50-$100x10^9$/L, investigator will take the decision to stop or not romiplostim according to patient's risk of bleeding. This decision will be always taken after discussion with the study coordinator.

If patient needs treatment again it will be prescribed according to routine clinical practice. In romiplostim is used, it will not be supplied by the sponsor.

In the ROM+DEX arm, dexamethasone will be administered 40 mg daily x 4 days only in the first cycle. Gastric protection alongside dexamethasone is

recommended. Romiplostim first dose could be administrated day 1, 2, 3 or 4 of first cycle of dexamethasone.

In the DEX arm, dexamethasone will be administered 40 mg daily x 4 days for up to 3 cycles every 14 to 28 days. No dose adjustment for dexamethasone is permitted. Gastric protection alongside dexamethasone is recommended.

Once romiplostim or dexamethasone is stopped after 365 days since randomization, patients should be clinically evaluated minimum every 4±1 weeks for 6 months (180 days) and continuation of treatment should be decided on an individual basis by the treating physician. At specified visits outlined in the Study Schedule, patients will undergo physical exams including measurement of vital signs (respiratory rate, body temperature, blood pressure, and pulse rate), height (only at screening visit) and weight, blood counts with absolute and relative differential (neutrophil, lymphocyte and monocyte) blood chemistry profiles (serum creatinine, ALT, AST, GGT, K, Na, LDH), platelet counts, haemoglobin counts as well as review of adverse events and serious adverse events. Measurements of treatment response, health-related quality of life, and other measurements of efficacy per SOC will be collected.

In this study approximately126 patients will participate. They will be enrolled in 30study sites from Spain, United Kingdom and Italy.

### i. Disease

Primary Immune thrombocytopenia

### j. Study outcome measures

Primary outcome measure:

To evaluate the difference between study arms in the proportion of patients achieving 6mSROT-50 at 6 months (180 days) from treatment cessation.

- Definition of 6mSROT-50: platelets higher or equal than $50x10^9$/L in the absence of any ITP treatment including any rescue treatment for at least 6 consecutive months (≥180 days) from treatment cessation and without WHO grade 2 or more bleeding.

Secondary outcome measures:

- To evaluate the difference between study arms in the proportion of patients achieving 6mSROT-30 at 6 months (180 days) from treatment cessation.
    - Definition of 6mSROT-30: platelets higher or equal than $30x10^9$/L in the absence of any ITP treatment including any rescue treatment for at least 6 consecutive months (≥180 days) from treatment cessation and without WHO grade 2 or more bleeding.

- To evaluate the difference between study arms in the proportion of patients achieving 12mSROT-50 at 12 months (365 days) from treatment cessation.
    - Definition of 12mSROT-50: platelets higher or equal than $50x10^9$/L in the absence of any ITP treatment including any rescue treatment for at least 12 consecutive months (≥365 days) from treatment cessation and without WHO grade 2 or more bleeding.
- To evaluate the difference between study arms in the proportion of patients achieving 12mSROT-30 at 12 months (365 days) from treatment cessation.
    - Definition of 12mSROT-30: platelets higher or equal than $30x10^9$/L in the absence of any ITP treatment including any rescue treatment for at least 12 consecutive months (≥365 days) from treatment cessation and without WHO grade 2 or more bleeding.
- To evaluate the difference between study arms in the proportion of patients with complete response (CR) at 6 months (Day 180), at 12 months (Day 365) from randomisation and at End of study Visit (visit 12 months after the last dose of study treatment). We will evaluate this in the total sample and in the absence of any rescue treatment
    - Definition of CR: platelet count ≥$100x10^9$/L and absence of bleeding symptoms.
- To evaluate the difference between study arms in the proportion of patients with response (R) at 6 months (Day 180), at 12 months (Day 365) from randomisation and at End of study Visit (visit 12 months after the last dose of study treatment).We will evaluate this in the total sample and in the absence of any rescue treatment
    - Definition of R: platelet count between $100x10^9$/L and $30x10^9$/L and at least doubled from baseline and absence of bleeding symptoms.
- To evaluate the difference between study arms in the proportion of patients with global response (GR) at 6 months (Day 180), at 12 months (Day 365) from randomisation and End of study Visit (visit 12 months after the last dose of study treatment). We will evaluate this in the total sample and in the absence of any rescue treatment
    - Definition of GR: CR or R.
- To evaluate the difference between study arms in the proportion of patients with response within the target range (TR) at 6 months (Day 180), at 12 months (Day 365) from randomisation and End of study Visit (visit 12 months after the last dose of study treatment).We will evaluate this in the total sample and in the absence of any rescue treatment
    - Definition of TR: platelet count between ≥$30x10^9$/L and ≤$400x10^9$/L.

- To evaluate the difference between study arms in the median time to first response defined as the time from randomization to first response (R) in the absence of any rescue treatment. We will evaluate this in the total sample and in the absence of any rescue treatment.
- To evaluate the difference between study arms in the proportion of patients with early response (ER) and initial response (IR).
    - Definition of ER: proportion of patients with platelet count higher or equal than $30x10^9$/L and at least doble than baseline at first week (Day 7) from randomisation.
    - Definition of IR: proportion of patients with platelet count higher or equal than $30x10^9$/L in the first month (Day 30) from randomisation.
- To compare the difference of means between study arms of the maximum number of consecutive days with platelet response (CR, R, GR and TR) along the study period. We will evaluate them in the total sample and in the absence of any rescue treatment
- To compare the difference of means between study arms of the total number of days with platelet response (CR, R, GR and TR) along the study period. We will evaluate them in the total sample and in the absence of any rescue treatment.
- To evaluate and to compare the proportion of patients who need rescue treatments and proportion and time to treatment failures.
- To compare the time to loss of response (LoR) in patients who achieved response in both arms.
    - Definition of LoR: number of days from the first time the patient achieved a platelet count ≥$30x10^9$/L until platelet count dropped below $30x10^9$/L measured on 2 occasions with more than 1 day apart or presence of bleeding
- To compare the difference between study arms in the proportion of patients requiring any rescue treatment along the study period.
- To compare the difference between study arms in the proportion of patients with adverse events (AEs), including serious adverse events (SAEs) and laboratory safety parameters. AEs will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Bleeding events will be carefully monitored.
- To compare the difference between study arms in the mean change in patients' bleeding from screening to Day 1, Week 8, Week 12, Moth 6, Moth 12andEnd of study Visit (visit 12 months after the last dose of study treatment) assessed with the ITP-bleeding tool in both arm.
- To compare the difference between study arms in the mean change in patients' quality of life from baseline Day 1 (the day of administration of the first dose of study medication) to Week 8, Month 6 (Day 180), Month12 (Day 365) from randomisation and End of study Visit (visit 12 months after

the last dose of study treatment) assessed with SF-36v2, FACIT-F and ITP-PAQ in both arms.

- To describe and compare the difference between study arms in mean of healthcare resources use (HRU) from treatment initiation to end of study (outpatient visits and home health care, hospitalizations and emergency visits, diagnostic procedures, pharmacological and non-pharmacological treatments and HRU related to management of adverse drug reactions) and loss of productivity (number of days of absenteeism from school or work and associated cost).

### k. Study population and number of patients

Investigators will be expected to maintain a screening log of all potential study candidates. Eligibility criteria will be evaluated during screening.

Before any study-specific activity/procedure, the appropriate written informed consent must be obtained.

Prospective approval of protocol deviations to recruitment and enrolment criteria will not be provided.

The primary endpoint of this study is the 6mSROT-50 (≥50x$10^9$/L) rate at 6 months from treatment cessation. In patients with newly diagnosed primary immune thrombocytopenia treated with dexamethasone 40 daily x 4 days for one to three cycles, 6mSROT-50 (≥50x$10^9$/L) at 6 months from treatment cessation has been assumed to be 30% [2]. The sample size was based on the assumption that ROM + DEX can improve sustained response at 6 months from treatment cessation up to 56.6% similarly to eltrombopag plus dexamethasone as described by Zhang[2]. A total of 63 patients/arm are required to achieve 80% power to detect a difference with a two-sided significance level of 5%, if the true 6mSROT-50 rates at 6 months from treatment cessation are 30% in the DEX arm and 56,6% in the ROM + DEX arm and assuming a dropout rate of 15%. The total minimal size is 126 patients to be randomized.

### l. Selection criteria

#### i. Inclusion criteria

1. Age ≥ 18 years of age at the time of signing informed consent.
2. Newly diagnosis of primary ITP according to the International Working Group assessment [1] and previously untreated for ITP.
3. Platelet counts <30x$10^9$/L or ITP with platelet counts <50x$10^9$/L and concomitant bleeding symptoms.

4. Serum creatinine concentration ≤1.5 mg/dL.

**ii. Exclusion criteria**

1. WHO performance status >2.
2. Previous therapy with rituximab (within 3 months previous of study enrollment), corticosteroids or therapy with other immunomodulating agents within 1 month before enrolment; prior use of hematopoietic analogs or fostamatinib for any other reason than ITP three months before enrolment.
3. Previous use of romiplostim, PEG-recombinant human (rHu) megakaryocyte growth and development factor, eltrombopag, recombinant human anti-thrombopoietin (rHuTPO), or any platelet-producing agent for three months prior to enrolment.
4. Alkylating agents within 8 weeks before the screening visit or anticipated use during the time of the proposed study.
5. Splenectomy within 3 months of the screening visit or planned splenectomy during study period.
6. Abnormal renal function (serum creatinine > 1.5 mg/dL).
7. Active hepatic disease evidenced by alanine aminotransferase [ALT] or aspartate aminotransferase [AST] levels >5 times the upper limit of normal (it will only be necessary to determine one of the two transaminases).
8. Severe chronic liver disease as evidenced by, but not limited to, any of the following: International Normalized Ratio (INR) > 1.4, hypoalbuminemia, portal vein hypertension including presence of otherwise unexplained splenomegaly and history of esophageal varices.
9. Patients with known IgM seropositive tests for cytomegalovirus and/or Epstein-Barr virus in the previous month.
10. Patients with an active viral infection at screening for Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), detectable virus charge of HIV
11. Intolerance to dexamethasone.
12. History of a bone marrow stem cell disorder.
13. Active or prior malignancy except adequately treated (i.e., complete surgical excision with negative margins) basal cell carcinoma in the last 5 years.
14. History of Helicobacter pylori by urea breath test or stool antigen test within 6 months of enrolment, if available.
15. History of myelodysplastic syndrome, systemic lupus erythematosus, or autoimmune cytopenia.

16. History of antiphospholipid antibody syndrome.
17. History of disseminated intravascular coagulation, hemolytic uremic syndrome, or thrombotic thrombocytopenic purpura.
18. History of deep or superficial venous thromboembolism in the last 12 months or stroke, acute ischaemic heart disease or acute peripheral vascular disease in the last 6 months.
19. Hypersensitivity to any recombinant Escherichia coli-derived product (e.g., Infergen, Neupogen, Somatropin, and Actimmune) or known sensitivity to any of the products to be administered during dosing
20. Currently enrolled in another investigational device or drug study or < 30 days since ending another investigational device or drug studies, or receiving other investigational agents.
21. Will have any other investigational procedures performed while enrolled in this clinical study.
22. Pregnant or breastfeeding, or planning to become pregnant or breastfeed during treatment or within 1 month after the end of treatment
23. Female subject of childbearing potential is not willing to use, in combination with her partner, an acceptable method of effective contraception during treatment and for 1 month after the end of treatment (see annex 5 for additional contraception information). Females of childbearing potential should only be included after a negative pregnancy test.
24. Will not be available for protocol-required study visits, to the best of the subject's and investigator's knowledge
25. Any kind of disorder that, in the opinion of the investigator, may compromise the ability of the subject to give written informed consent and/or to comply with all required study procedures
26. Other serious comorbidities at investigator criteria.

### *m.* Study calendar

First patient inclusion: Last quarter 2022

Last patient inclusion: First quarter 2024

Subject participation duration: 24 months

# 2. TABLE OF CONTENTS

## 3. ABBREVIATIONS

| Abbreviation | Full terminology |
|---|---|
| 6mSROT-30 | SROT with platelets higher or equal than $30x10^9$/L for 6 months |
| 6mSROT-50 | SROT with platelets higher or equal than $50x10^9$/L for 6 months |
| 12mSROT-30 | SROT with platelets higher or equal than $30x10^9$/L for 12 months |
| 12mSROT-50 | SROT with platelets higher or equal than $50x10^9$/L for 12 months |
| AE | Adverse Event |
| AESI | Adverse Event of Special Interest |
| ALT | Alanine aminotransferase |
| ASH | American Society for Hematology |
| AST | Aspartate aminotransferase |
| CBC | Complete Blood Counts |
| CI | Confidence Interval |
| CP | Complete Response |
| CPK | Creatinine Phosphokinase |
| CR | Complete Response |
| CRF | Case Report Form |
| CRA | Clinical Research Associate |
| CRO | Clinical Research Organization |
| CSR | Clinical Study Report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DEX | Dexamethasone |

| Abbreviation | Full terminology |
|---|---|
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Form |
| EDC | Electronic Data Capture |
| EOS | End Of Study |
| EOT | End of Treatment |
| EQ-5D-5L | 5-level European Quality of Life–5 Dimensions |
| ER | Early Response |
| eTPO | Endogenous Thrombopoietin |
| FSH | Follicle-Stimulating Hormone |
| GCP | Good Clinical Practice |
| GGT | Gamma-Glutamyl Transferase |
| GR | Global Response |
| HBV | Hepatitis B Virus |
| HIV | Human Immunodeficiency Virus |
| HRU | Health Resource Utilization |
| ICF | Informed Consent Form |
| ICH | International Council for Harmonisation |
| IEC | Independent Ethics Committee |
| IVIg | Intravenous Immunoglobulin |
| IgM | Immunoglobulin M |
| INR | International Normalized Ratio |
| IP | Investigational Product |
| IR | Initial Response |

| Abbreviation | Full terminology |
|---|---|
| IRB | Institutional Review Board |
| ITP | Immune Thrombocytopenia |
| ITP-BAT | Immune Thrombocytopenia - Bleeding Assessment Tool |
| IUD | Intrauterine device |
| IUS | Intrauterine hormonal-releasing system |
| IV | Intravenous |
| K | Potassium |
| Kg | Kilogram |
| L | Liter |
| LDH | Lactate Dehydrogenase |
| LoR | Loss of Response |
| MedDRA | Medical Dictionary for Regulatory Activities |
| Mg | Milligram |
| Mcg | Microgram |
| mM | Micromolar |
| Na | Sodium |
| NASH | Nonalcoholic Steatohepatitis |
| PR | Partial Response |
| QC | Quality Control |
| R | Response |
| rHU | Recombinant Human |
| rHuTPO | Recombinant human anti-thrombopoietin |
| ROM | Romiplostim |

| Abbreviation | Full terminology |
|---|---|
| S | Skin |
| SC | Subcutaneous |
| SAE | Serious Adverse Event |
| SD | Standard Deviation |
| SMOG | Gradation of Severity |
| SOC | Standard of Care |
| SOP | Standard Operating Procedures |
| SR | Sustained Response |
| SROT | Sustained Response Off any ITP Treatment |
| TBL | Total Bilirubin |
| TBC | To Be Concrete |
| TPO | Thrombopoietin |
| TR | Response within the Target Range |
| ULN | Upper Limit of Normal |
| WHO | World Health Organisation |

# 4. CLINICAL TRIAL CHARACTERISTICS

### *a.* Clinical trial identification

**Code:** RODEX

**Title:** A multicentre, randomized, open-label study of romiplostim plus dexamethasone vs dexamethasone in patients with newly diagnosed primary immune thrombocytopenia.

### b. Phase

Phase III

### c. Investigational product

Romiplostim and dexamethasone

### d. Sponsor

**Sponsor**

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### e. Ethics Committee

SPAIN: Comité de Ética de la Investigación con medicamentos Provincial de Sevilla.

ITALY: Comitato Etico dell'Università "Sapienza"

UNITED KINGDOM: Wales Research Ethics Committee 1 Cardiff (REC number: 23/WA/0199).

### *f.* Study calendar

First patient inclusion: Last quarter 2022

Last patient inclusion: First quarter 2024

Subject participation duration: 18 months

Study duration: 24 months

## 5. STUDY RATIONALE AND OBJECTIVES

### a. Background information

#### *i.* Disease

Primary immune thrombocytopenia (ITP) is an acquired disease that causes thrombocytopenia through an immunological mechanism [1,3].The estimated incidence of ITP is around 2-6 per 100,000 children/year and approximately 2-4 per 100,000 adults/year [4–6]. The primary manifestation of ITP is an increased tendency to bleed, which varies from cutaneous purpura to more severe mucosal bleeding [7].

ITP is characterized by a low circulating platelet counts ($<100\times10^9$/L) caused by platelet destruction and diminished platelet production [1]. The traditional understanding of the disease was that low levels of circulating platelets are a result of antibodies binding to platelet antigens, which leads to destruction of platelets in the reticuloendothelial system, primarily the spleen [8–11].

However, it is now understood that ITP is a more complex disease process, involving impaired platelet production and T-cell-mediated mechanisms, in addition to antibody-mediated platelet destruction [12]. Thrombocytopenia places patients at risk for bruising, mucocutaneous bleeding, and, more seriously, intracranial hemorrhage.

The traditional classification of chronic and acute ITP in the literature is based solely on persistence of thrombocytopenia from time of diagnosis, where acute ITP is defined as <6 months and chronic ITP is defined as >6 months from original diagnosis [13].

In 2009, an international working group proposed three distinct ITP phases [1]: newly diagnosed (≤3 months after diagnosis), persistent (>3–12 months after diagnosis), and chronic (after >12 months) [7,14,15].

These new ITP definitions represented a move away from the historical classification of chronic ITP as lasting longer than 6 months. It is a recognition of the fact that there is still a substantial proportion of patients who will undergo spontaneous remission during the first 12 months of their disease, but fewer do so after 1 year [1,7,16–18]. Accordingly, the division into three phases reflects the clinical observation that ITP changes with duration, with spontaneous remission becoming less likely as the duration of disease increases [1,7,17,18].

### *ii.* Current Treatments for ITP

The European Joint Working Group guidelines note that for newly diagnosed ITP, without or with only mild bleeding (WHO 0–II) and platelet values >$20\times10^9$/L–$30\times10^9$/L, a 'watch and wait' strategy would be appropriate; however, treatment should not be denied if that is the wish of the patient [7].

Short course of corticosteroids is recommended as first-line treatment [7,14,15,19]. Most patients respond to corticosteroids with a rise in platelet count, but improvements are usually transient and the majority of patients will relapse [7,19].

Although prolonged corticosteroid therapy may maintain a haemostatic platelet count in responding patients, it does not enhance the rate of remission [7,20] and long-term use is linked with a number of side effects that can be serious, distressing to the patient, so the duration of corticosteroid therapy should be minimized.

Updated ASH guidelines recommend administering corticosteroids for 6-8 weeks (treatment plus taper) [15], either prednisone or dexamethasone for initial treatment. The International Consensus Report recommends a maximum of 3 weeks of high-dose prednisolone or three cycles of dexamethasone for initial treatment of newly diagnosed patients [14].

On the other hand, the European Joint Working Group recommends three regimens in adults: 1–2 weeks of oral or intravenous (IV) prednisone or prednisolone (then tapered); 1–5 days of IV methylprednisolone (then prednisone tapering); or 4–6 biweekly or monthly cycles of 4 days of dexamethasone [7].

Corticosteroids may be accompanied by intravenous immunoglobulin (IVIg) for patients with serious/life-threatening bleeding or ahead of surgery but provide a short platelet response [3]. IVIg can be used where corticosteroids are contraindicated [18].

Most patients respond to the initial treatment with corticosteroids and/or IVIg/anti-D immunoglobulin, but the majority will relapse and require subsequent therapy [7,19]. Guidelines recommends delay the introduction of splenectomy for ≥ 12–

24 months [7,14,15,19] in contrast to prior guidelines in which the decision to use TPO-RAs was often only after splenectomy failure or in the chronic phase.

### iii. Benefit / risk assessment

The risks are those inherent in the usual treatment of ITP, the benefit is the earlier access to the use of thrombopoietin analogues, reducing the long-term side effects of steroids, which have been shown to be greater than those of steroids. In addition, the potential benefit is that the early combination of two types of ITP treatment that act via different pathways may improve ITP treatment outcomes by reducing the rate of chronicity, which with steroid monotherapy is 60% at 6 months post-treatment cessation

### *iv.* Romiplostim

The indications for romiplostim have recently been updated. Romiplostim is indicated for the treatment of primary immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments (e.g., corticosteroids, immunoglobulins).

Romiplostim is a peptibody that includes a carrier domain (IgG1 Fc portion) and a peptide-containing domain (four peptides, each comprising 14 amino acids, designed to activate the TPO receptor [c-mpl; TPO-R] but avoid production of antibodies that can bind to endogenous TPO) [21–23] due to romiplostim has no amino acid sequence homology to endogenous TPO (eTPO). The peptides bind to the extracytoplasmic domain of the TPO-R and activate the receptor similarly to that of endogenous TPO, meaning that romiplostim and endogenous TPO compete for receptor binding [22,23].

For a complete summary of safety and efficacy data collected for the romiplostim clinical development program, please refer to the most recent version of the Investigator's Brochure.

#### *Clinical efficacy and safety*

In clinical trials, treatment with romiplostim resulted in dose-dependent increases in platelet count. Time to reach the maximum effect on platelet count is approximately 10-14 days, and is independent of the dose. After a single subcutaneous dose of 1 to 10 mcg/kg romiplostim in ITP patients, the peak platelet count was 1.3 to 14.9 times greater than the baseline platelet count over a 2 to 3 weeks period and the response was variable among patients. The platelet counts of ITP patients who received6 weekly doses of 1 or 3 mcg/kg of romiplostim were within the range of 50 to $450x10^9$/L for most patients.

#### *Results from pivotal placebo-controlled studies*

The safety and efficacy of romiplostim was evaluated in two placebo-controlled, double-blind studies in adults with ITP who had completed at least one treatment

prior to study entry and are representative of the entire spectrum of such ITP patients.

Study S1 evaluated patients who were non-splenectomised and had an inadequate response or were intolerant to prior therapies. Patients had been diagnosed with ITP for approximately 2 years at the time of study entry. Patients had a median of 3 (range, 1 to 7) treatments for ITP prior to study entry. Prior treatments included corticosteroids (90% of all patients), immunoglobulins (76%), rituximab (29%), cytotoxic therapies (21%), danazol (11%), and azathioprine (5%). Patients had a median platelet count of $19x10^9$/L at study entry.

Study S2 evaluated patients who were splenectomised and continued to have thrombocytopenia. Patients had been diagnosed with ITP for approximately 8 years at the time of study entry. In addition to a splenectomy, patients had a median of 6 (range, 3 to 10) treatments for ITP prior to study entry. Prior treatments included corticosteroids (98% of all patients), immunoglobulins (97%), rituximab (71%), danazol (37%), cytotoxic therapies (68%), and azathioprine (24%). Patients had a median platelet count of $14x10^9$/L at study entry.

Both studies were similarly designed. Patients (≥ 18 years) were randomised in a 2:1 ratio to receive a starting dose of romiplostim 1 mcg/kg or placebo. Patients received single subcutaneous weekly injections for 24 weeks. Doses were adjusted to maintain (50 to $200x10^9$/L) platelet counts. In both studies, efficacy was determined by an increase in the proportion of patients who achieved a durable platelet response. The median average weekly dose for splenectomised patients was 3mcg/kg and for non-splenectomised patients was 2mcg/kg. A significantly higher proportion of patients receiving romiplostim achieved a durable platelet response compared to patients receiving placebo in both studies. Following the first 4 weeks of study romiplostim maintained platelet counts ≥ $50x10^9$/L in between 50% to 70% of patients during the6 month's treatment period in the placebo-controlled studies. In the placebo group, 0% to 7% of patients were able achieve a platelet count response during the 6 months of treatment.

In an open-label randomised 52 weeks trial [24] in adult subjects received romiplostim or medical standard of care (SOC) treatment. This study evaluated non-splenectomised patients with ITP and platelet counts < $50x10^9$/L. Romiplostim was administered to 157 subjects by subcutaneous (SC) injection once weekly starting at a dose of 3 mcg/kg (mean (±SE) weekly dose 3.9± 2.1 mcg/kg), and adjusted throughout the study within a range of 1-10 mcg/kg in order to maintain platelet counts between 50 and $200x10^9$/L, 77 subjects received SOC treatment according to standard institutional practice or therapeutic guidelines.

The overall subject incidence rate of splenectomy was 8.9% (14 of 157 subjects) in the romiplostim group compared with 36.4% (28 of 77 subjects) in the SOC group, with an odds ratio (romiplostim vs SOC) of 0.17 (95% CI: 0.08, 0.35).

The overall subject incidence of treatment failure was 11.5% (18 of 157 subjects) in the romiplostim group compared with 29.9% (23 of 77 subjects) in the SOC group, with an odds ratio (romiplostim vs SOC) of 0.31 (95% CI: 0.15, 0.61).

In summary, clinical trials have shown that romiplostim leads to platelet responses (platelet count >50×$10^9$/L at any visit) in most patients with ITP (79–95%) and these responses are sustained over time [24–28]. These studies also showed that romiplostim is well tolerated [24–28].

Data from nine clinical trials were integrated to compare outcomes for patients with ITP ≤1 year or >1 year. Results from patients with ITP ≤1 year or >1 year who received romiplostim, placebo or standard of care (SOC) after failing first line treatments were analyzed [29]. Studies were conducted between 2002 and 2014 and included 311 patients with ITP ≤1 year (155 with newly diagnosed ITP and 156 with persistent ITP and 726 with chronic ITP. Platelet counts, decrease in rescue medication use, and reduction in bleeding were all similar between romiplostim treated patients with ITP ≤1 versus >1 year. Overall, the results of this integrated analysis show that romiplostim is as efficacious in patients with newly diagnosed or persistent ITP as in those with chronic ITP.

### *v.* Dexamethasone

A short course of corticosteroids is recommended as first-line treatment in patient with ITP by guidelines [7,14,15,19]. One of the three regimens recommended by the European Joint Working Group is 4-6 biweekly or monthly cycles of 4 days of dexamethasone [7].

To evaluate efficacy of three-period pulses of high-dose dexamethasone, adult naïve ITP patients for 3 months from diagnosis with a count of platelet <30×$10^9$/L or more than 30×$10^9$/L with the signs of bleeding existence based on bleeding grading scores were included were randomly assigned to receive prednisone or a three-pulse regimen of high-dose dexamethasone. In high-dose dexamethasone group, 40 mg of dexamethasone was administered for 4 consecutive days and was repeated in 14-day intervals for three pulses of treatment. Patients in the prednisone group received 1.0 mg/kg of prednisone orally per day for 4 consecutive weeks. The initial response rate of platelet count in the high-dose dexamethasone group was significantly higher than the prednisone group. The initial and sustained response (SR) rate of platelet count in the high-dose dexamethasone group was significantly higher. In fact, in the high-dose dexamethasone group, more patients reached SR after the 8-month follow-up. These results suggest that a three-pulse high-dose dexamethasone regimen could be better to achieve the SR and overall response without the burden of long-term corticosteroid consumption and concludes that in patients with ITP who have not received any kind of treatment, high-dose dexamethasone was more effective than conventional prednisone therapy [30].

On the other hand, a systematic review and meta-analysis of randomized controlled trials using dexamethasone or prednisolone showed a higher incidence of sustained response favourable to dexamethasone when used more than one course of dexamethasone or tapering corticosteroids. The overall response at day 28 was also significantly improved with dexamethasone. In addition, there were also significantly fewer adverse events in the dexamethasone arm and the study concluded that use of dexamethasone instead of prednisolone may be more beneficial as the initial therapy for ITP patients [31].

***vi.*** **Dexamethasone plus eltrombopag**

Another study [2] compared dexamethasone alone vs a regimen of eltrombopag plus pulsed dexamethasone as first-line therapy. Sustained response off therapy was defined as maintaining platelet counts >50x$10^9$/L for more than six months without further ITP therapy. 56.6% patients achieved the primary endpoint and this was statistically superior that the assumed response rate of 30% with dexamethasone alone.

**b. Study rationale**

Primary immune thrombocytopenia (ITP) is a disease that results from autoimmune destruction of platelets and suppression of platelet production[32]. Newly diagnosed ITP is considered as lasting up to 3 months, followed by persistent (3-12 months) and chronic disease (12 months) [33]. Frontline therapy includes corticosteroids and intravenous immunoglobulin (IVIg). Prednisone at a dose of 1 to 2 mg/kg raises platelet count in 70% to 80% of patients; however, only a small portion achieves a sustained remission [12]. High-dose dexamethasone is initially effective in 85% of patients. Nevertheless, 50% relapse within the first 6 months [33–35]. Despite corticosteroids remain the standard of care, the high failure/relapse rates and considerable adverse effects from long-term use stimulates the search for better treatments [12,35,36]. Sustained response (SR) rates ranging from 58 to 78% using rituximab plus dexamethasone as frontline therapy have been reported [37–41]. There is little experience regarding the use of thrombopoietin analogues as first line treatment. Gómez-Almaguer et al [42] described a 66.7% of relapse free survival after 12 months of absence of eltrombopag treatment in patients with newly diagnosed ITP.

This study aims to evaluate dexamethasone and romiplostim combination as first line treatment in newly ITP patients to improve SROT avoiding bleeding, corticosteroids toxicity and necessity of rescue treatments.

**c. Study objectives**

Primary objective:

To evaluate the superiority of romiplostim plus dexamethasone vs dexamethasone alone after 6 months (≥180 days) from treatment cessation in patients with newly primary immune thrombocytopenia (ITP) in terms of sustained

response off any ITP treatment (6mSROT-50) and without WHO grade 2 or more bleeding.

Maximum time on treatment with romiplostim will be 12 months (365 days). Then, patients will be followed up for 6 additional months (180 days) after stopping romiplostim.

Secondary objectives:

- To evaluate the superiority of romiplostim plus dexamethasone vs dexamethasone alone after 6 months (≥180 days) from treatment cessation in patients with newly primary immune thrombocytopenia in terms of sustained response off any ITP treatment (6mSROT-30) from treatment cessation and without WHO grade 2 or more bleeding.
- To evaluate the superiority of romiplostim plus dexamethasone vs dexamethasone alone after 12 months (≥365 days) from treatment cessation, if data available, in patients with newly primary immune thrombocytopenia in terms of sustained response off any ITP treatment (12mSROT-30 and 12mSROT-50) from treatment cessation and without WHO grade 2 or more bleeding.
- To evaluate the superiority of romiplostim plus dexamethasone vs dexamethasone alone in terms of complete response (CR), response (R) global response (GR) and response within the target range (TR) at 6 months (Day 180), at 12 months (Day 365) from randomisation and End of study Visit (visit 12 months after the last dose of study treatment). We will evaluate them in the who trial cohort but also in a subgroup that excludes patients receiving any rescue treatment. Or an additional sensitivity analysis will exclude patients receiving rescue treatment.
- To compare the time to first response defined as the time from randomization to first response (R) in both arms. We will evaluate this in the total sample and in the absence of any rescue treatment.
- To compare the proportion of patients with early response (ER) and initial response (IR) in both arms.
- To compare the duration of platelet response assessed as: the maximum number of consecutive days with platelet response (CR, R, GR and TR) and, the total number of days along the study period with platelet response (CR, R, GR and TR) in both arms. We will evaluate them in the total sample and in the absence of any rescue treatment.
- To compare the time to loss of response (LoR) in patients who achieved response in both arms.
- To compare the proportion of patients requiring any rescue treatment along the study period in both arms

- To evaluate and compare proportion of treatment failure and time to treatment failure.
- To evaluate the safety and tolerability of study treatments in both arms.
- To compare the difference between study arms in the mean change in patients' bleeding
- To compare the change in patients' quality of life from baseline Day 1(the day of administration of the first dose of study medication) to 2 (Week 8), Month 6 (Day 180), Month 12 (Day 365) and End of study Visit (visit 12 months after the last dose of study treatment) assessed with SF-36 v2, FACIT-F and ITP-PAQ in both arms.
- To describe and compare healthcare resources use (HRU) and loss of productivity in both study arms.

# 6. STUDY DESIGN

## a. Overall design

This is an open label, randomized, phase 3 study designed to compare romiplostim plus dexamethasone vs dexamethasone alone in terms of sustained response off any ITP treatment in adult subjects (≥18 years old) with newly diagnosed of ITP.

According to the International Working Group assessment [1] patients will be screened for study participation. Subjects who meet eligibility criteria will be enrolled. Once eligibility is confirmed, patient will be randomized, Randomization will be stratified by center with a 1:1 allocation using random block sizes, to receive dexamethasone 40 mg daily x 4 days only in the first cycle and subcutaneous romiplostim weekly for up to 12 months (ROM + DEX arm) or dexamethasone 40 mg daily x 4 days for up to 3 cycles every 14 to 28 days (DEX arm).

The monitoring will be the same in both arms with slight differences to allow for dose adjustments of romiplostim:

- In the ROM + DEX arm, patients will be reviewed weekly for 8 weeks (56 days). After week 8, patients will be reviewed every 2 weeks (14 days) for 8 additional weeks and then monthly until week 52 (365 days) from randomization.
    - If romiplostim dose should be modified, patients will be reviewed weekly until a stable dose of romiplostim is reached for at least 4 weeks (28 days). After that, patients will go on with visits every 2 weeks (14 days) for 8 weeks and then monthly until Week 52 (365 days) from randomization.
- In the DEX arm, patients will be reviewed weekly until the completion of dexamethasone cycles and for a minimum of 8 weeks (56 days). After that,

every 2 weeks (14 days) for 8 additional weeks and then monthly until Week 52 (365 days) from randomization.

The following assessments will be done in these visits: platelets count, bleeding score, number and characteristics of bleeds, adverse events, study medication, rescue medication and concomitant medication, HRU associated with the ITP or its treatment and lost productivity (days of absentee in scholarship or work and presentism).

Quality of life will be evaluated at Day 1 (the day of administration of the first dose), Month2 (Day 60), Month 6 (Day 180) Month12 (Day 365) and End of study Visit (visit 12 months after the last dose of study treatment). See Study schedule for more details.

In the ROM+DEX arm, starting romiplostim dose will be 3 mcg/kg, adjusting the following weekly doses according to platelet counts following actual label indications (see section Dosage and administration, for more detailed information). Romiplostim first dose could be administrated day 1, 2, 3 or 4 of first cycle of dexamethasone. Patients will weekly receive dose increases of romiplostim in increments of 1 mcg/kg up to a maximum dose of 10 mcg/kg aiming for a platelet count higher than $50x10^9$/L. If romiplostim dose is stable for 4 weeks and platelets are higher than $50x10^9$/L, romiplostim will be tapered in 1 mcg/kg per week to a dose of 1 mcg/kg per week. If after 4 additional weeks, platelets remain greater than 50, the Interval between 1mcg/kg romiplostim injections will increase to 14 days. If after 4 doses of romiplostim 1 mcg/kg/14 days, platelets remain still higher than $50x10^9$/L treatment with romiplostim could be ended. Any way, if platelets are between 50-$100x10^9$/L, investigator will take the decision to stop or not romiplostim according to patient's risk of bleeding. This decision will be always taken after discussion with the study coordinator. If platelets are lower than $50x10^9$/L treatment with romiplostim will go on.

In the ROM + DEX arm, if platelets counts are lower than $20x10^9$/L or bleeding symptoms related to thrombocytopenia are present between romiplostim doses, rescue therapy with intravenous immunoglobulin (IVIg) can be used at doses described in Rescue medication section. It would be considered treatment failure if platelets are lower than $30x10^9$/L after 4 weeks with romiplostim at 10mcg/kg/week or rescue medication is needed to get this level of platelets despite this dose of 10mcg/kg/week for 4 weeks.

In the ROM + DEX arm, dexamethasone will be administered 40 mg daily x 4 days only in the first cycle. Gastric protection alongside dexamethasone is recommended. Romiplostim first dose could be administrated day 1, 2, 3 or 4 of first cycle of dexamethasone.

In the DEX arm, dexamethasone will be administered 40 mg daily x 4 days for up to 3 cycles every 14 to 28 days. No dose adjustment for dexamethasone is permitted. Gastric protection alongside dexamethasone is recommended.

In the DEX arm, if platelet counts are lower than $20x10^9$/L or bleeding symptoms related to thrombocytopenia are present between cycles, rescue therapy with IVIg (maximum dose 2 gr/kg during 1 to 5 days) or low doses of prednisone (0,5 mg/kg/d) could be used. If patients use rescue treatment with prednisone low doses, they should be decreased as soon as possible in a maximum of 8 weeks. It would be considered treatment failure if platelets are lower than $30x10^9$/L after 3 cycles of dexamethasone or rescue medication is needed to get this level of platelets despite the 3 cycles of dexamethasone.

Once romiplostim or dexamethasone is stopped or after 365 days since randomization, patients should be clinically evaluated minimum every 4±1 weeks for 6 months (180 days) and continuation of treatment should be decided on an individual basis by the treating physician. If patient needs treatment again it will be prescribed according to routine clinical practice. If romiplostim is used, it will not be supported by the sponsor.

At specified visits outlined in the Study Schedule, patients will undergo physical exams including measurement of vital signs (respiratory rate, body temperature, blood pressure, and pulse rate), height (only at screening visit) and weight, blood counts with absolute and relative differential (neutrophil, lymphocyte and monocyte)blood chemistry profiles (serum creatinine, ALT, AST, GGT, K, Na, LDH), platelet counts, haemoglobin counts as well as review of adverse events and serious adverse events. Measurements of treatment response, health-related quality of life, and other measurements of efficacy per SOC will be collected.

In this study approximately 126 patients will participate. They will be enrolled in 30 study sites from Spain, United Kingdom and Italy.

**b. Primary endpoint**

Primary outcome measure:

To evaluate the difference between study arms in the proportion of patients achieving 6mSROT-50 at 6 months (180 days) from treatment cessation.

- Definition of 6mSROT-50: platelets higher or equal than $50x10^9$/L in the absence of any ITP treatment including any rescue treatment for at least 6 consecutive months (≥180 days) from treatment cessation and without WHO grade 2 or more bleeding.

**c. Secondary endpoints**

Secondary outcome measures:

- To evaluate the difference between study arms in the proportion of patients achieving 6mSROT-30 at 6 months (180 days) from treatment cessation.
    - Definition of 6mSROT-30: platelets higher or equal than $30x10^9$/L in the absence of any ITP treatment including any rescue treatment

for at least 6 consecutive months (≥180 days) from treatment cessation and without WHO grade 2 or more bleeding.

- To evaluate the difference between study arms in the proportion of patients achieving 12mSROT-50 at 12 months (365 days) from treatment cessation.
    - Definition of 12mSROT-50: platelets higher or equal than $50x10^9$/L in the absence of any ITP treatment including any rescue treatment for at least 12 consecutive months (≥365 days) from treatment cessation and without WHO grade 2 or more bleeding.
- To evaluate the difference between study arms in the proportion of patients achieving 12mSROT-30 at 12 months (365 days) from treatment cessation.
    - Definition of 12mSROT-30: platelets higher or equal than $30x10^9$/L in the absence of any ITP treatment including any rescue treatment for at least 12 consecutive months (≥365 days) from treatment cessation and without WHO grade 2 or more bleeding.
- To evaluate the difference between study arms in the proportion of patients with complete response (CR) at 6 months (Day 180), at 12 months (Day 365) from randomisation and End of study Visit (visit 12 months after the last dose of study treatment). We will evaluate this in the total sample and in the absence of any rescue treatment
    - Definition of CR: platelet count ≥$100x10^9$/L and absence of bleeding symptoms.
- To evaluate the difference between study arms in the proportion of patients with response (R) at 6 months (Day 180), at 12 months (Day 365) from randomisation and End of study Visit (visit 12 months after the last dose of study treatment).We will evaluate this in the total sample and in the absence of any rescue treatment
    - Definition of R: platelet count between $100x10^9$/L and $30x10^9$/L and at least doubled from baseline and absence of bleeding symptoms.
- To evaluate the difference between study arms in the proportion of patients with global response (GR) at 6 months (Day 180), at 12 months (Day 365) from randomisation and End of study Visit (visit 12 months after the last dose of study treatment). We will evaluate this in the total sample and in the absence of any rescue treatment
    - Definition of GR: CR or R.
- To evaluate the difference between study arms in the proportion of patients with response within the target range (TR) at 6 months (Day 180), at 12 months (Day 365) from randomisation and End of study Visit (visit 12

months after the last dose of study treatment).We will evaluate this in the total sample and in the absence of any rescue treatment

  - Definition of TR: platelet count between ≥30x$10^9$/L and ≤400x$10^9$/L.

- To evaluate the difference between study arms in the median time to first response defined as the time from randomization to first response (R) in the absence of any rescue treatment. We will evaluate this in the total sample and in the absence of any rescue treatment.
- To evaluate the difference between study arms in the proportion of patients with early response (ER) and initial response (IR).
  - Definition of ER: proportion of patients with platelet count higher or equal than 30x$10^9$/L and at least doble than baseline at first week (Day 7) from randomisation.
  - Definition of IR: proportion of patients with platelet count higher or equal than 30x$10^9$/L in the first month (Day 30) from randomisation.
- To compare the difference of means between study arms of the maximum number of consecutive days with platelet response (CR, R, GR and TR) along the study period. We will evaluate them in the total sample and in the absence of any rescue treatment
- To compare the difference of means between study arms of the total number of days with platelet response (CR, R, GR and TR) along the study period. We will evaluate them in the total sample and in the absence of any rescue treatment.
- To evaluate and to compare the proportion of patients who need rescue treatments and proportion and time to treatment failures
- To compare the time to loss of response (LoR) in patients who achieved response in both arms.
  - Definition of LoR: number of days from the first time the patient achieved a platelet count ≥30x$10^9$/L until platelet count dropped below 30x$10^9$/L measured on 2 occasions with more than 1 day apart or presence of bleeding
- To compare the difference between study arms in the proportion of patients requiring any rescue treatment along the study period.
- To compare the difference between study arms in the proportion of patients with adverse events (AEs), including serious adverse events (SAEs) and laboratory safety parameters. AEs will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Bleeding events will be carefully monitored.
- To compare the difference between study arms in the mean change in patients' bleeding from screening to Day 1, to Week 8, Week 12, Month 6,

Month 12 and End of study Visit (visit 12 months after the last dose of study treatment) with the ITP-bleeding assessment tool in both arm.

- To compare the difference between study arms in the mean change in patients' quality of life from baseline Day 1, (the day of administration of the first dose of study medication) to 2 (week 8), 6 months (Day 180), 12 months (Day 365) and End of study Visit (visit 12 months after the last dose of study treatment) assessed with SF-36 v2, FACIT-F and ITP-PAQ in both arm.
- To describe and compare the difference between study arms in mean of healthcare resources use (HRU) from treatment initiation to end of study (outpatient visits and home health care, hospitalizations and emergency visits, diagnostic procedures, pharmacological and non-pharmacological treatments and HRU related to management of adverse drug reactions) and loss of productivity (number of days of absenteeism from school or work and associated cost).

## 7. PATIENT SELECTION

Investigators will be expected to maintain a screening log of all potential study candidates. Eligibility criteria will be evaluated during screening.

Before any study-specific activity / procedure, the appropriate written informed consent must be obtained.

Prospective approval of protocol deviations to recruitment and enrollment criteria will not be provided.

### a. Inclusion criteria

1. Age ≥ 18 years of age at the time of signing informed consent.
2. Newly diagnosis of primary ITP according to the International Working Group assessment [1]and previously untreated for ITP.
3. Platelet counts $<30x10^9$/L or ITP with platelet counts $<50x10^9$/L and concomitant bleeding symptoms.
4. Serum creatinine concentration ≤1.5 mg/dL.

### b. Exclusion criteria

1. WHO performance status >2.
2. Previous therapy with rituximab (within 3 months previous of study enrollment), corticosteroids or therapy with other immunomodulating agents within 1 month before enrolment; prior use of hematopoietic analogs or fostamatinib for any other reason than ITP three months before enrolment.

3. Previous use of romiplostim, PEG-recombinant human (rHu) megakaryocyte growth and development factor, eltrombopag, recombinant human anti-thrombopoietin (rHuTPO), or any platelet-producing agent for three months prior to enrolment.
4. Alkylating agents within 8 weeks before the screening visit or anticipated use during the time of the proposed study.
5. Splenectomy within 3 months of the screening visit or planned splenectomy during study period.
6. Abnormal renal function (serum creatinine > 1.5 mg/dL).
7. Active hepatic disease evidenced by alanine aminotransferase [ALT] or aspartate aminotransferase [AST] levels >5 times the upper limit of normal (it will only be necessary to determine one of the two transaminases).
8. Severe chronic liver disease as evidenced by, but not limited to, any of the following: International Normalized Ratio (INR) > 1.4, hypoalbuminemia, portal vein hypertension including presence of otherwise unexplained splenomegaly and history of esophageal varices.
9. Patients with known IgM seropositive tests for cytomegalovirus and/or Epstein-Barr virus in the previous month.
10. Patients with an active viral infection at screening for Hepatitis B Virus (HBV), Hepatitis C Virus (HCV) or detectable virus charge of HIV.
11. Intolerance to dexamethasone.
12. History of a bone marrow stem cell disorder.
13. Active or prior malignancy except adequately treated (i.e., complete surgical excision with negative margins) basal cell carcinoma in the last 5 years.
14. History of Helicobacter pylori by urea breath test or stool antigen test within 6 months of enrollment, if available.
15. History of myelodysplastic syndrome, systemic lupus erythematosus, or autoimmune cytopenia.
16. History of antiphospholipid antibody syndrome.
17. History of disseminated intravascular coagulation, hemolytic uremic syndrome, or thrombotic thrombocytopenic purpura.
18. History of deep or superficial venous thromboembolism in the last 12 months or stroke, acute ischaemic heart disease or acute peripheral vascular disease in the last 6 months.
19. Hypersensitivity to any recombinant Escherichia coli-derived product (e.g., Infergen, Neupogen, Somatropin, and Actimmune) or known sensitivity to any of the products to be administered during dosing

20. Currently enrolled in another investigational device or drug study or < 30 days since ending another investigational device or drug studies, or receiving other investigational agents.
21. Will have any other investigational procedures performed while enrolled in this clinical study.
22. Pregnant or breastfeeding, or planning to become pregnant or breastfeed during treatment or within 1 month after the end of treatment.
23. Female subject of childbearing potential is not willing to use, in combination with her partner, an acceptable method of effective contraception during treatment and for 1 month after the end of treatment (see annex 5 for additional contraception information). Females of childbearing potential should only be included after a negative pregnancy test.
24. Will not be available for protocol-required study visits, to the best of the subject's and investigator's knowledge.
25. Any kind of disorder that, in the opinion of the investigator, may compromise the ability of the subject to give written informed consent and/or to comply with all required study procedures.
26. Other serious comorbidities at investigator criteria.

**c. Randomization procedures**

Each subject who enters into the screening period for the study (when the subject signs the informed consent) will receive a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned by the eCRF. This subject identification number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

Subjects who are determined not eligible after screening must be screen-failed in the eCRF and the reason for the screen failure provided.

Upon confirmation of eligibility, the site staff will use the eCRF to randomise a subject. Randomization of the patient is authorized until 72 hours after signing the informed consent. Randomization will be stratified by center with a 1:1 allocation using random block sizes to receive:

- Dexamethasone 40 mg daily x 4 days only in the first cycle and subcutaneous romiplostim weekly (ROM + DEX arm) for up to 12 months (365 days).
- Dexamethasone 40 mg daily x 4 days for up to 3 cycles every 14 to 28 days (DEX arm).

The investigator is responsible to document the decision to enroll the patient into the study and will note and date the information in the subject's medical record and in/on the enrolment CRF. Subjects will be considered enrolled upon randomization in the eCRF. The subject identification number must remain constant throughout the entire clinical study.

Romiplostim will be sent to the site upon subject screening.

### d. Blinding procedures

Not applicable. Open label study.

## 8. WITHDRAWAL CRITERIA

### a. Screening failure

Screening failures are patients who do not fulfill the eligibility criteria for the study, and therefore must not be enrolled and randomised. These patients should have the reason for study withdrawal recorded as "eligibility criteria not fulfilled". This reason for study withdrawal is not valid for randomized patients.

Patients can be rescreened a single time, but they cannot be re-randomized.

### b. Reasons for Withdrawal

Patients may withdraw from treatment at any time.

The Investigator may discontinue study treatment for any of the following reasons:

- Patient desires the discontinuation of treatment (i.e., withdraws consent for treatment).
- No response to study treatment.
- Adverse event that, in the opinion of the investigator or the sponsor, contraindicates further dosing.
- Pregnancy or intention to become pregnant.
- Subject noncompliance that, in the opinion of the investigator or sponsor, warrants withdrawal; e.g., refusal to adhere to scheduled visits.
- Noncompliance with study procedures.
- Intercurrent illness or worsening of a chronic condition.

The primary reason for withdrawal from treatment will be documented in the eCRF.

If the reason for withdrawal is an AE, the patient will be followed by the Investigator until such events resolve, stabilize, and, according to the Investigator's judgment, there is no need for further follow-up.

A patient who withdraws consent will always be asked about the reason for withdrawal and the presence of any AE. The Investigator will follow up AEs outside of the clinical study.

If a patient withdraws from participation in the study, then his or her randomization or patient identification number cannot be reused. Withdrawn patients will not be replaced.

Reasons for removal of a subject from the study are:

- Decision by sponsor
- Withdrawal of consent from study
- Death
- Lost to follow-up
- No response – treatment failure

### c. Handling of Withdrawals

Subjects who are permanently discontinued from receiving study treatment will be followed for safety, including the collection of any protocol-specified information, unless consent is withdrawn or the subject is lost to follow-up. All subjects will be followed for 12 months since randomization, and minimum 6 months after stopping the study treatment (both arms).

The investigator will be requested to collect all patient data until he/she left the study.

### d. Lost to follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fail to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or is able to continue in the study.
- In cases in which the subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject

(where possible, 3 telephone calls). These contact attempts are to be documented in the subject's medical record.

- If the subject continues to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

#### e. Reserve and Replacement Subjects

Randomised subjects will not be replaced.

#### f. Prematurely termination or suspension of the study

This study may be temporarily suspended or prematurely terminated by the sponsor if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the sponsor to the IRB/IEC and Health Authorities.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping.
- Insufficient compliance to protocol requirements.
- Data that are not sufficiently complete and/or evaluable.
- Determination of futility.

## 9. INVESTIGATIONAL PRODUCT

Romiplostim and dexamethasone are the investigational medicinal products for this study.

Sponsor will provide romiplostim and dexamethasone to study sites.

#### a. Investigational product description

##### i. Description

**Romiplostim**

Romiplostim for injection is supplied as a sterile, preservative-free, lyophilized, solid white powder for subcutaneous injection.

**Dexamethasone**

Dexamethasone is supplied as uncoated tablets for oral administration.

### ii. Packaging

**Romiplostim**

Romiplostim will be manufactured and packaged by Amgen Inc. Romiplostim is supplied in a 5mL single-use vial as a sterile, white, preservative-free, lyophilized powder containing a protein concentration of 0.5 mg/mL of 10 mM histidine, 4.0% mannitol, 2.0% sucrose, and 0.004% polysorbate 20 and has a pH 5.0 when reconstituted with 1.2 mL of sterile water for injection.

Romiplostim will be manufactured by Alcura Health España:

C/ Marie Curie, 54 · Poligono Can Alemany

08840 Viladecans, · Barcelona, · Spain

**Dexamethasone**

Dexamethasone will be manufactured and packaged byAlcura Health España:

C/ Marie Curie, 54 · Poligono Can Alemany

08840 Viladecans, · Barcelona, · Spain.

Dexamethasone will be administered orally by 40mg tablets, with a total of 4 or 12 tablets per blister.

### iii. Shipping, Storage and Disposal

**Romiplostim**

Romiplostim should be stored in a refrigerator (2ºC–8ºC). Do not freeze. Store in the original carton in order to protect from light.

Romiplostim may be removed from the refrigerator for a period of 30 days at room temperature (up to 25ºC) when stored in the original carton.

Romiplostim is a sterile but unpreserved medicinal product and is intended for single use only. Romiplostim should be reconstituted in accordance with good aseptic practice.

After reconstitution: Chemical and physical in-use stability has been demonstrated for 24 hours at 25ºC and for 24 hours at 2ºC – 8ºC, when protected from light and kept in the original vial.

From a microbiological point of view, the medicinal product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 25ºC or 24 hours in a refrigerator (2ºC – 8ºC), protected from light.

After dilution: Chemical and physical in-use stability has been demonstrated for 4 hours at 25ºC when the diluted product was held in a disposable syringe, or 4

hours in a refrigerator (2ºC – 8ºC) when the diluted product was held in the original vial.

From a microbiological point of view, the diluted romiplostim should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 4 hours at 25ºC in disposable syringes, or 4 hours in a refrigerator (2ºC – 8ºC) in the original vials, protected from light.

**Dexamethasone**

Dexamethasone does not require special storage conditions in terms of temperature. Store in the original pack to protect from light and moisture.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

### b. Dosage and administration

**Romiplostim**

Romiplostim will be administered in the clinic by a qualified healthcare provider as a subcutaneous (SC) injection until the patient is ready to self-administer, according to medical criterion. Self-administration will be registered in medical records. In the ROM+DEX arm, starting romiplostim dose will be 3 mcg/kg, adjusting the following weekly doses according to platelet counts following actual label indications.

**<u>Dosage calculation</u>**

The starting dose of romiplostim is 3mcg/kg which is calculated based on current body weight (Table 1).

**Table 1. Romiplostim dose calculation**

| | |
|---|---|
| Initial or subsequent doses once a a week | Weight* (kg) x dose (mcg/kg) = individual patient dose (mcg) |
| Volume of administration: | $\text{Doses (mcg)} \times \frac{1\ ml}{500\ mcg} = quantity\ to\ be\ injected\ (ml)$ |
| Example: | • The starting dose for a 75 kg patient is 3mcg/kg romiplostim.<br>• Individual patient dose= 75 kg x 3mcg/kg = 225 mcg<br>• Corresponding amount of romiplostim solution to be injected:<br>$225\ \text{mcg} \times \frac{1\ ml}{500\ mcg} = 0{,}45\ ml\ to\ be\ injected$ |

**The current body weight of the patient at the time of initiation of treatment should always be used when calculating the dose of romiplostim. Future dose adjustments should be based solely on changes in platelet counts and should be made in 1 mcg/kg increments.*

**Dosage adjustment**

**Table 2 Dose adjustments and tapering**

| **platelet counts** | **Romiplostim dosage adjustment** |
|---|---|
| Platelets <50x10$^9$/L | Increase 1mcg/kg/week to a maximum of 10mcg/kg/week |
| Platelets 50-250x10$^9$/L | No change in dose.<br>Drug tapering:<br>o If 4 consecutive weeks with stable dose, reduce romiplostim in 1mcg/kg/week.<br>o If stable dose during 4 weeks is 1mcg/kg/week, reduce romiplostim to 1mcg/kg/14 days.<br>o If stable dose is 1mcg/kg/14 days after 4 doses stop romiplostim |
| Platelets >250x10$^9$/L | Stop romiplostim and platelet control weekly.<br>o Restart romiplostim when platelets < 150x10$^9$/L<br>o Restart romiplostim at 1mcg/kg/weekly less than previous |

1. The starting dose should be 3 mcg/kg/week*. It could be start during de 4 days of dexamethasone. This dosage is due to:
    - The patient profile, on whom it is urgent to achieve an effective treatment as soon as possible.
    - Current clinical practice. PTI Spanish clinical guideline [43] recommends starting with a dose of 5-10 mcg/kg in urgent cases. In the Spanish PTI guideline also it is stated that *"although Romiplostim is initiated according to prescribing information at a dose of 1 µg/kg/week subcutaneously, most patients require doses of 3 µg/kg/week to respond, so in clinical practice it is usually initiated at 3 µg/kg/week, reaching a maximum dose of 10 µg/kg/week."*
    - Other clinical study [44] with similar patient profiles the median dose (Q1-Q3) of romiplostim was 2,6(1,6-3,9)mcg/kg.

**Since the starting dose of romiplostim will be 3 mcg/kg instead of 1 mcg/kg as indicated in the label, close monitoring of potential safety concerns will be conducted.*

2. Patients will weekly receive dose increases of romiplostim in increments of 1 mcg/kg up to a maximum dose of 10 mcg/kg in an attempt to reach a target platelet count higher than $50x10^9$/L.
    - If romiplostim dose is stable for 4 weeks and platelets are higher than $50x10^9$/L, romiplostim will be tapered in 1 mcg/kg per week up to a dose of 1 mcg/kg per week.
    - If after 4 additional weeks patients still present platelet counts higher than $50x10^9$/L with romiplostim 1 mcg/kg, romiplostim will be indicated as 1 mcg/kg/14 days.
    - If after 4 doses of romiplostim 1 mcg/kg/14 days, platelets remain still higher than $50x10^9$/L treatment with romiplostim should be ended.
3. Otherwise, if platelets are lower than $50x10^9$/L treatment with romiplostim will go on until Day 365 since randomization.

If platelets are between 50-$100x10^9$/L, investigator will take the decision to stop or not romiplostim according to patient's risk of bleeding. This decision will be always taken after discussion with the study coordinator.

**Dexamethasone**

Dexamethasone will be given to the patient for oral administration at home.

In the ROM + DEX arm, dexamethasone will be administered 40 mg daily x 4 days only in the first cycle

In the DEX arm, dexamethasone will be administered 40 mg daily x 4 days for up to 3 cycles every 14 to 28 days.

The use of commercial dexamethasone will be authorized up to 3 days, in case the patient is attended in emergency care while the criteria for the study are being checked and labeled study medication is assigned.

### c. Treatment duration and monitoring

The monitoring will be the same in both arms with slight differences to allow for dose adjustments of romiplostim:

- In the ROM + DEX arm patients will be reviewed weekly for 8 weeks (56 days). After Week 8, patients will be reviewed every 2 weeks (14 days) for 8 additional weeks and then monthly until Week 52 (Month 12) from randomization.

- If romiplostim dose should be modified, patients will be reviewed weekly until a stable dose of romiplostim is reached for at least 4 weeks (28 days). After that, patients will go on with visits every 2 weeks (14 days) for 8 weeks and then monthly until Week 52(Month 12) from randomization.

- In the DEX arm, patients will be reviewed weekly until the completion of dexamethasone cycles and for a minimum of 8 weeks (56 days). After that, every 2 weeks (14 days) for 8 additional weeks and then monthly until Week 52 (Month 12) from randomization.

Once romiplostim or dexamethasone is stopped or after 365 days since randomization, patients should be clinically evaluated minimum every 4+/- 1 week for 12 months and continuation of treatment should be decided on an individual basis by the treating physician.

If patient needs treatment again it will be prescribed according to routine clinical practice. In case romiplostim is used, it will not be supported by the sponsor.

### d. Criteria for dose adjustments

Dose adjustments for romiplostim will be based on platelet count as described in previous Dosage and administration section.

No dose adjustment for dexamethasone is permitted.

### e. Rescue medication

We will consider rescue medication IVIg, platelet transfusion or prednisone. Tranexamic acid will be not considered rescue medication. Rescue medication will be used as follow:

- In the ROM + DEX arm, if platelets counts are lower than $20x10^9$/L or bleeding symptoms related to thrombocytopenia are present between romiplostim doses, rescue therapy with IVIg(maximum dose 2 gr/kg in total during 1 to 5 days) can be used. Prednisolone is not allowed in this arm.
- In the DEX arm, if platelet counts are lower than $20x10^9$/L or bleeding symptoms related to thrombocytopenia are present between cycles, rescue therapy with IVIg (maximum dose 2 gr/kg in total during 1 to 5 days) or low doses of prednisone (0,5 mg/kg/d) can be used. If patients use rescue treatment with prednisone, they should be decreased as soon as possible and stopped within 8 weeks.

### f. Treatment failure

In the ROM + DEX arm, it would be considered treatment failure if platelets are lower than $30x10^9$/L after 4 weeks with romiplostim at 10 mcg/kg/week or rescue

medication is needed to get this level of platelets despite this dose of 10mcg/kg/week for 4 weeks.

In DEX arm, it would be considered treatment failure if platelets are lower than $30x10^9$/L after 3 cycles of dexamethasone or if rescue medication is needed to get this level of platelets despite the 3 cycles of dexamethasone.

In both arms, treatment failure will be considered to in those patients bleeding who are refractory to therapy in whom it is considered clinically in their best interests to escalate or switch treatment in a way that does not align with the protocol treatment schedules. Patients will be discussed with Steering Committee before to be considered treatment failure.

If patients lose response on the DEX arm, they can be switched from one arm to the other (to TPO-RA), but outside the trial. The treatment will be provided by their centre and this information will be collected up in the CRF. The patients will be considered a treatment failure.

### g. Accountability

The study medication (i.e., romiplostim, dexamethasone) will be sent directly from the sponsor to the investigator's site pharmacy preceded by the Regulatory Green Light. The medication is to be used exclusively in the clinical trial according to the instructions of this study protocol.

When a drug shipment is received, the Investigator or designee will check the amount and condition of the delivery, drug expiration date, and sign the Receipt of Shipment Form provided. The Receipt of Shipment Form should be faxed or sent by e-mail to the CRO. The original form will preliminarily be retained at the site and will be collected at the next monitoring visit by the monitor and stored in the TMF at CRO. A copy will remain in the Investigator File at the site. In case of shipment problems, the Investigator or designee shall contact the CRA as soon as possible.

An Investigational Product Accountability Log will be provided for the trial medication. The record must be continuously updated and contain the dates, quantities and compounds of drugs received, medication identification number(s), the patient identification number to whom the trial medication was dispensed, date and quantity of medication dispense and the initials of the dispenser.

### h. Concomitant medication

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care, except for those listed in section *Prohibited drugs.*

For concomitant therapies therapy name, indication, dose, unit, frequency, route, start date and stop date will be recorded.

Reduction or discontinuation of permitted concurrent ITP therapies may begin once a subject's platelet count has increased to ≥50x$10^9$/L.

Rescue medication will also be collected.

Concomitant therapies are to be collected from screening through the EOS visit, as applicable.

#### i. Prohibited drugs

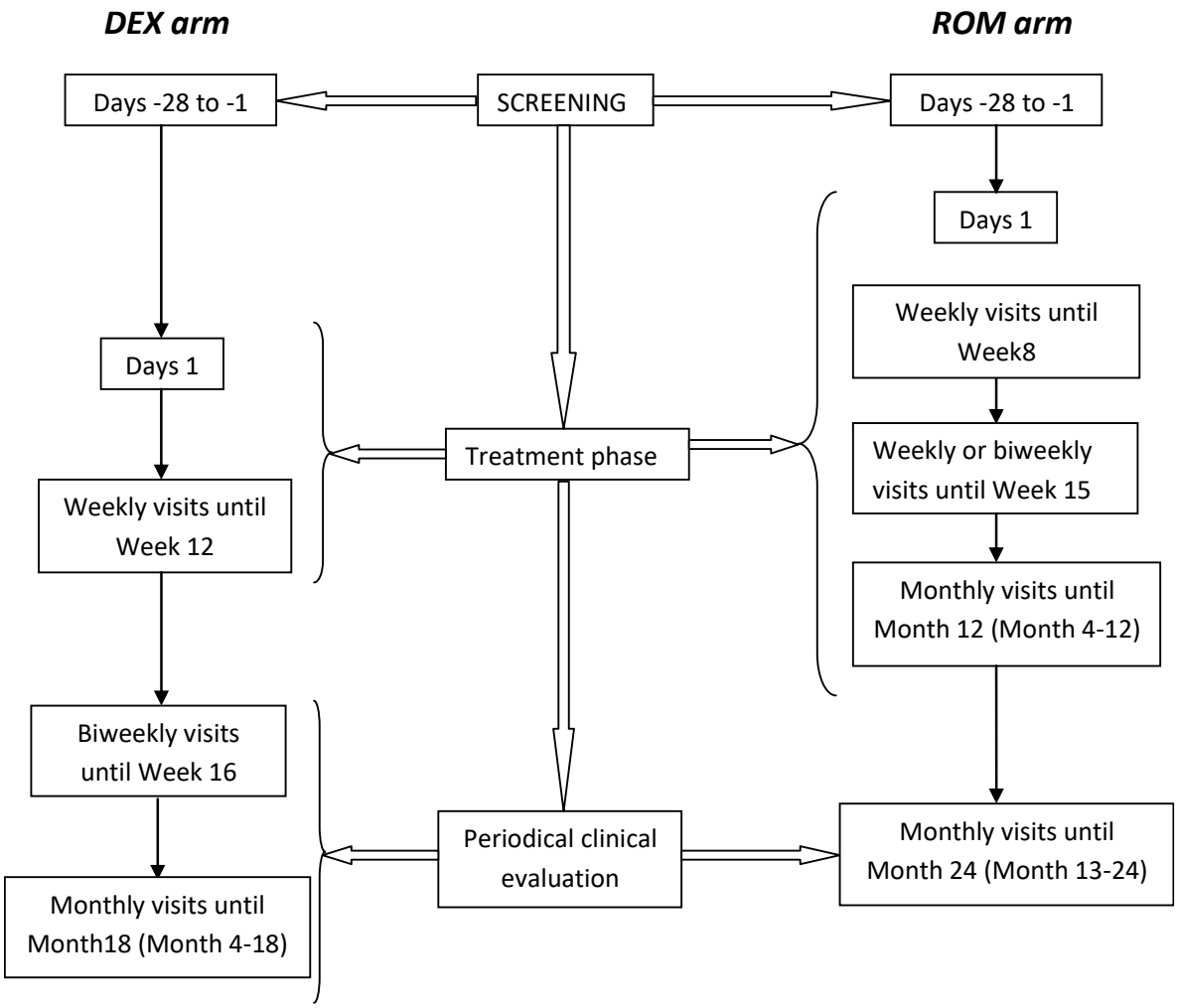
The following medications are not permitted during this study. After treatment failure, they will be allowed:

- Other thrombopoietic receptor agonists
- Any cytotoxic agents, alkylating agents
- Rituximab
- rHuTPO
- Interferon
- Herbal supplements that are associated with bleeding side effects including, but not limited to, gingko biloba, garlic, ginseng, fish oil, dong quai, feverfew. Garlic and ginseng taken through a normal diet are not excluded.
- Aspirin at doses higher than 100mg or anticoagulant drugs.
- Treatments for ITP other than allowed rescue medications (includings plenectomy).
- Any other investigational agents that are not approved

Should a subject require administration of any of the medications listed above, sponsor should be consulted before the medication is administered, when possible. In all cases, sponsor must be informed within 24 hours. Sponsor may decide that the subjects will be ineligible to receive additional administrations of study medication.

# STUDY SCHEDULE AND STUDY FLOW-CHART

## Study flow-chart



## Table 3. Schedule of study assessments.

## *DEX arm*

| Visit number<br>Study time point | Visit 0<br>Screening | Visit 1<br>Baseline | Visit 2- 8 | Visit 9 | Visit 10, 11, 12, 13 and 15 | Visit 17-18 | Visit 19 | Visit 20-24 | Visit 25 | Visit 26-36<br>(Periodical clinical evaluation after the end of study medication[11]) | Visit 37<br>(End of study Visit)[12] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Days -28 to -1 | Day 1 | Weekly visits until Week 7 | Week 8 | Weekly or biweekly visits until Week 14[11] | Week 16 and week 20 | Week 24 (Month 6) | Monthly visits until Month 11 | Month 12 | Monthly visits until Month 17[12] | Month 18[12] | Unscheduled visit |
| | | | ±1 days | ±1 days | ±1 days | ±3 days | ±7 days | ±3 days | ±7 days | ±7 days | ±7days | |
| Eligibility criteria | X | x | | | | | | | | | | |
| Informed consent[1] | X | | | | | | | | | | | |
| Medical history[3] | X | | | | | | | | | | | |
| Demographics[2] | X | | | | | | | | | | | |
| Pregnancy test[4] | X | | | | | | | | | | | |
| Randomization | | X | | | | | | | | | | |
| Vital signs[5] | X | X | X | X | X[5] | X | X | X | X | X | X | X |
| Physical examination[6] | X | X | X[6] | X | X[6] | X | X | X | X | X | X | X |
| Laboratory tests[7] | X | X | X | X | X | X | X | X | X | X | X | X |
| WHO Bleeding score | X | X | X | X | X | X | X | X | X | X | X | X |
| HRU and loss of productivity[8] | X | X | X | X | X | X | X | X | X | X | X | |
| Quality of life questionnaires:[9] SF36, FACIT, ITP PAQ | | X | | X | | | X | | X | | X | |
| ITP-BAT[10] | X | X | | X | X[10] | | X | | X | | X | |
| ITP medication | | X | X | X | X | X | X | X | X | | | |
| Rescue medication | | X | X | X | X | X | X | X | X | | | X |
| Concomitant medication | | X | X | X | X | X | X | X | X | X | X | X |
| AEs/Bleeding event reporting//splenectomy | | X | X | X | X | X | X | X | X | X | X | X |

*1. Informed consent must be signed and dated prior to any study-related procedure and before any data is recorded in the CRF.*

*2. Demographic data collection including sex, age, and ethnicity.*

*3. Medical history includes all information related to a new diagnosis of ITP and bleeding events history.*

*4. The pregnancy test at screening will be conducted 72 hours before first dose of study treatment.*

*5. Vital signs includes respiratory rate, body temperature, blood pressure, and pulse rate. They must be measured every week until week 8, then every 4 weeks.*

*6. Physical examination will be performed as per standard of care. Physical measurements include height (at screening) and weight (at screening, baseline and from then on every 4 weeks+/- 1 week). There shall be no dose adjustments until changes of 10% or more in weight.*

*7. Complete blood counts with differential, blood chemistry profiles (serum creatinine, ALT, AST, GGT, K, Na, LDH) and platelet counts.*

*8. HRU and loss of productivity shall be measured monthly.*

*9. Quality of life (SF36 v2, FACIT-F and IPT-PAQ) will be evaluated at Day 1, week 8, Month 6, Month 12 and End of study Visit (visit 12 months after the last dose of study treatment).*

*10. ITP-BAT will be evaluated to screening, Day 1, Week 8, Week 12, Month 6, Month 12 and End of study Visit (visit 12 months after the last dose of study treatment).*

*11. In the DEX arm, patients will be reviewed every 14 days for 2 months (until Week 16). In the ROM + DEX arm patients will be reviewed weekly if romiplostim dose is changed. If a stable dose of romiplostim is reached or it has been stopped, patient will be reviewed every 14 days for 2 months (until Week 15) (see 9.c Treatment duration and monitoring).*

*12. Once romiplostim or dexamethasone is stopped, patients should be clinically evaluated periodically for 12 months after the treatment stops (see 9.c Treatment duration and monitoring).*

# Romiplostim arm

| Visit number<br>Study time point | Visit 0<br>Screening | Visit 1<br>Baseline | Visit 2- 8 | Visit 9 | Visit 10-16 | Visit 17-18 | Visit 19 | Visit 20-24 | Visit 25<br>(End of study treatment Visit, if not ended before) | Visit 26-36<br>(Periodical clinical evaluation after the end of study medication[11]) | Visit 37<br>(End of study Visit)[12] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Days -28 to -1 | Day 1 | Weekly visits until Week 7 | Week 8 | Weekly or biweekly visits until Week 15[11] | Week 16 and week 20 | Week 24 (Month 6) | Monthly visits until Month 11 | Month 12 | Monthly visits until Month 23[12] | Month 24[12] | Unscheduled visit |
| | | | ±1 days | ±1 days | ±1 days | ±3 days | ±7 days | ±3 days | ±7 days | ±7 days | ±7days | |
| Eligibility criteria | X | x | | | | | | | | | | |
| Informed consent[1] | X | | | | | | | | | | | |
| Medical history[3] | X | | | | | | | | | | | |
| Demographics[2] | X | | | | | | | | | | | |
| Pregnancy test[4] | X | | | | | | | | | | | |
| Randomization | | X | | | | | | | | | | |
| Vital signs[5] | X | X | X | X | X[5] | X | X | X | X | X | X | X |
| Physical examination[6] | X | X | X[6] | X | X[6] | X | X | X | X | X | X | X |
| Laboratory tests[7] | X | X | X | X | X | X | X | X | X | X | X | X |
| WHO Bleeding score | X | X | X | X | X | X | X | X | X | X | X | X |
| HRU and loss of productivity[8] | X | X | X | X | X | X | X | X | X | X | X | |
| Quality of life questionnaires:[9] SF36, FACIT, ITP PAQ | | X | | X | | | X | | X | | X | |
| ITP-BAT[10] | X | X | | X | X[10] | | X | | X | | X | |
| ITP medication | | X | X | X | X | X | X | X | X | | | |
| Rescue medication | | X | X | X | X | X | X | X | X | | | X |
| Concomitant medication | | X | X | X | X | X | X | X | X | X | X | X |
| AEs/Bleeding event reporting//splenectomy | | X | X | X | X | X | X | X | X | X | X | X |

*1. Informed consent must be signed and dated prior to any study-related procedure and before any data is recorded in the CRF.*

*2. Demographic data collection including sex, age, and ethnicity.*

*3. Medical history includes all information related to a new diagnosis of ITP and bleeding events history.*

*4. The pregnancy test at screening will be conducted 72 hours before first dose of study treatment.*

*5. Vital signs includes respiratory rate, body temperature, blood pressure, and pulse rate. They must be measured every week until week 8, then every 4 weeks.*

*6. Physical examination will be performed as per standard of care. Physical measurements include height (at screening) and weight (at screening, baseline and from then on every 4 weeks+/- 1 week). There shall be no dose adjustments until changes of 10% or more in weight.*

*7. Complete blood counts with differential, blood chemistry profiles (serum creatinine, ALT, AST, GGT, K, Na, LDH) and platelet counts.*

*8. HRU and loss of productivity shall be measured monthly.*

*9. Quality of life (SF36 v2, FACIT-F and IPT-PAQ) will be evaluated at Day 1, week 8, Month 6, Month 12 and End of study Visit (visit 12 months after the last dose of study treatment).*

*10. ITP-BAT will be evaluated to screening, Day 1, Week 8, Week 12, Month 6, Month 12 and End of study Visit (visit 12 months after the last dose of study treatment).*

*11. In the DEX arm, patients will be reviewed every 14 days for 2 months (until Week 16). In the ROM + DEX arm patients will be reviewed weekly if romiplostim dose is changed. If a stable dose of romiplostim is reached or it has been stopped, patient will be reviewed every 14 days for 2 months (until Week 15) (see 9.c Treatment duration and monitoring).*

*12. Once romiplostim or dexamethasone is stopped, patients should be clinically evaluated periodically for 12 months after the treatment stops (see 9.c Treatment duration and monitoring).*

### a. Study Assessments and Procedures

Study procedures and their time points are summarized in Study schedule (Table 3).

As protocol waivers or exemptions are not allowed if an enrolled subject is subsequently determined to be ineligible for the study, this must be discussed with the sponsor/principal investigator immediately upon occurrence or awareness to determine if the subject is to continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the Study schedule, is essential and required for study conduct.

#### i. Informed consent

All subjects or their legally authorized representative must sign and personally date the IRB/IEC approved informed consent before any study-specific procedures are performed.

Informed consent must be obtained before completing any screening procedure or discontinuation of standard therapy for any disallowed therapy. Each subject who enters into the screening period for the study (defined as the point when the subject signs the informed consent) will receive a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned by the eCRF. This subject identification number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

#### ii. Screening and enrolment

Screening will occur within 4 weeks of the commencement of the treatment period. The screening pregnancy test will be conducted 72 hours before first dose of treatment.

The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable. Subjects who are determined not eligible after screening must be screen-failed in the eCRF and the reason for the screen failure provided. Subjects may be enrolled or randomized only once into this study.

#### iii. Randomization

Randomisation is authorized until 72 hours after signing the consent form and after confirmation of fulfillment of all inclusion criteria and none of the exclusion criteria. In addition, the randomisation is authorised when the patient has received a maximum of 3 doses of in-hospital dexamethasone.

#### iv. Demographics

Demographic data collection including sex, age, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness.

### v. Medical History

Medical history will include information on the subject's concurrent medical conditions, including all information related to a new diagnosis of ITP, and bleeding event history. For subjects referred to the research centre, copies of the subject charts from the referring physician should be obtained. All findings should be recorded on the medical history eCRF. The current severity grade of conditions will be collected for those conditions that have not resolved.

### vi. Physical Examination

Physical examination will be performed as per standard of care and in accordance with the Study schedule. Physical examination findings should be recorded on the appropriate eCRF (e.g., medical history, event).

### vii. Physical Measurements

Height will be measured at screening. Weight will be measured at screening and from then on every 4 weeks+/-1 week. Height (in centimetres) and weight (kilograms) should be measured without shoes. There shall be no dose adjustments until changes of 10% or more in weight.

### viii. Vital signs

The following vital signs: respiratory rate, body temperature, blood pressure, and pulse rate will be measured at screening and in accordance with Study schedule. They must be measured every week until week 8, then every 4 weeks.

### ix. Platelet Counts

Platelet counts will be performed at each study visit, on a weekly basis during the treatment period and in the visits detailed in the Study schedule. Platelet counts will be evaluated by the investigative site’s local laboratory and used to assess the need for IP dose adjustments and to evaluate response to therapy.

### x. Bleeding Events

At every visit, subjects will be assessed for signs and symptoms of bleeding as well as details of any bleeding events that may have occurred since the last visit. Signs and symptoms of bleeding must be assessed as per the WHO grading scale [45]. Grading is based on physical examination at the time of the visit by the investigator. Bleeding events must be reported on the Event CRF.

### xi. Health Resource Utilization (HRU)

Data associated with health resource utilization will be collected in the eCRF for all subjects at selected time points). HRU and loss of productivity shall be measured monthly. Protocol-specified procedures are excluded.

The data collected may be used to conduct exploratory economic analyses and may include:

- Number and duration of medical care visits

- Home health care
- Hospitalization and duration of hospitalization
- Emergency room visits
- Number and type of diagnostic and therapeutic tests and procedures
- Outpatient medical treatments, pharmacological and non-pharmacological
- Loss of productivity (absenteeism from school or work)

### xii. Other Assessments

**ITP - bleeding assessment tool (ITP-BAT)**

The ITP-specific Bleeding Assessment Tool (ITP-BAT) was developed by the International Working Group on ITP as an instrument for more precise characterization of bleeding manifestations [46]. Characterization is based on standardized definitions of bleeding, symptom-specific and domain-specific grading, and a harmonised standardized questionnaire for adults and children.

Bleeding signs/symptoms are grouped according to three major domains: Skin (4 evaluations: petechiae; ecchymosis; subcutaneous hematomas; bleeding from minor wounds), Visible Mucosae (five evaluations: epistaxis; gum bleeding; haemorrhagic bullae/blisters; bleeding from bites to lips & tongue or after deciduous teeth loss/extraction; subconjunctival haemorrhage) and Organs (hematemesis, melena, haematochezia, rectorrhagia; haemoptysis, tracheobronchial bleeding; haematuria; menorrhagia; intramuscular hematoma; hemarthrosis; ocular bleeding; intracerebral, intraventricular, subarachnoidal, subdural, extradural; other internal bleedings).

Assessment is made for the worst episode during the observation period within a domain and is graded from 0 (No) to 4.

The ITP-BAT will be administered as detailed in the Study schedule.

**SF-36 v2.0**

The SF-36 is a 36-item scale constructed to survey health related QoLon 8 domains: limitations in physical activities due to heath problems; limitations in social activities due to physical or emotional problems; limitations unusual role activities due to physical health problems: limitations unusual role activities due to physical health problems; bodily pain; general mental health (psychological distress and well-being); limitations unusual role activities due to emotional problems; vitality (energy and fatigue); and general health perceptions. [47]

**FACIT-Fatigue Scale:**

The FACIT-Fatigue Scale is a short, 13-item, easy to administer tool that measures an individual´s level of fatigue during their usual daily activities over the past week. The level of fatigue is measured by recording item responses on a 4-point Likert scale ranging from 0 “not at all” to 4 “very much. [47]

**ITP Patient Assessment Questionnaire (ITP-PAQ):**

The ITP Patient Assessment Questionnaire™ (ITP-PAQ™) is a disease-specific instrument that was designed to measure the QoL of adult patients with immune thrombocytopenia. It is licensed for use in clinical studies through the Platelet Disorder Support Association. The instrument comprises 38 items completed by male respondents and 44 items completed by female respondents (Mathias 2007). The greater number of items for female respondents is due to additional questions dealing with the impact of ITP on the domains of women's reproductive health, menstrual symptoms and fertility. The shared domains are Activity, Bother, Fatigue, Fear, QoL, Psychological, Social activity and Symptoms. The items employ a 4-week recall with responses recorded on 4-, 5- or 7-point Likert scales. All item scores are transformed to a 0 to100 continuum where higher scores represent better QoL and are weighted equally to derive the scale scores. [48]

# 10. ASSESSMENT OF SAFETY / ADVERSE EVENTS

Safety information should be collected in clinical studies in an efficient and consistent way. Adverse events must be identified and notified rapidly to identify possible risks to patients and satisfy regulatory requirements for notification of adverse events. Safety reporting requirements to both Amgen and to Regulatory Agencies are specified. All reporting obligation to the Regulatory Authorities will be written and send.

## a. Definitions [49]

### i. Adverse event (AE)

An AE is any untoward medical occurrence in a patient participating in clinical research that is associated in time with the use of a medicinal product, whether or not it is considered to be related to the investigational products. Therefore, an adverse event can be any unfavourable and unintended sign (including an anomalous laboratory result), symptom or disease that is associated in time with the use of a medicinal product, whether or not it is considered to be related to the product. Pre-existing or underlying diseases that worsen during the study, or events associated with the discontinuation of the use of a product(s) (e.g. appearance of new symptoms), shall be notified as Adverse Events.

AEs include pre- or post-treatment events that occur as a result of study procedures (e.g. invasive procedures or modification of the patient's previous medication).

### ii. Serious adverse event (SAE)

A SAE is an undesired medical experience that, at any dose:

- Results in death.
- Is life-threatening: (NOTE: The term "life-threatening" refers to the fact that, according investigator criteria, the patient is at risk of death as a result of this

event. Nevertheless, this definition does not consider the situation in which if the AE had been more severe, patients had been in an immediate risk of death).

- Results in the patient's hospitalization or prolongs a previous hospitalization (NOTE: In general, hospitalization means that the patient has remained [at least 24 hours] in the hospital or emergency visits. Complications that occur during a hospitalization are AEs. If a complication prolongs hospitalization or satisfies any of the other criteria for seriousness, then the event will be considered SAE. When any doubt exists as to whether a "hospitalization" has taken place or was necessary, the AE will be considered serious. The hospitalization to implement scheduled treatment of a disease present before the subject entered the study and that has not worsened with respect to baseline is not considered an AE. Hospitalizations for social reason are not considering an AE.
- It produces disability or incapacity (NOTE: Disability refers to an important alteration in a person's capacity to carry out his or her own daily living tasks, not minor clinical ailments such as headaches, nausea, vomiting, diarrhoea, flu or accidental injuries (such as a sprained ankle), that can interfere with the functions of daily life, but do not alter them in an important way).
- It originates a congenital anomaly or birth defect.
- It is medically important, meaning medically important adverse event that the investigator regards as serious that did not strictly meet the criteria above but may have jeopardized the patient or required intervention to prevent one of the outcomes listed above, or that would suggest any significant hazard, contraindication, side effect, or precaution that may be associated with the use of the investigational medicinal product.

#### iii. Adverse reaction

Any harmful and non-intended response to a drug including adverse reactions derivative from any use apart from terms of commercialization authorization, abuse, and medication error. It exist a confirmed causality relationship with the administered medication.

### iv. Product Complaints

Any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug, combination product, or device after it is released for distribution to market or clinic by either: (1) Amgen or (2) distributors or partners for whom Amgen manufactures the material. This includes all components distributed with the drug, such as packaging, drug containers, delivery system, labelling, and inserts.

Examples include:

- Device that is damaged or broken
- Bent or blunt needles
- Missing or illegible labeling

- Inability of customer to administer the product
- Product with an unexpected color, appearance, or particles
- Use error (i.e., an act or omission of an act that results in a different combination product or medical device response than intended by the manufacturer or expected by the user, where the user attempted to use the combination product or medical device in good faith and experienced difficulty or deficiency administering the product).

### b. Characteristics of an adverse event

#### i. Seriousness

See Serious Adverse Event definition (11.1.2 Serious Adverse Event (SAE)).

#### ii. Causality assessment

The investigator has the obligation to establish the relation of causality between the investigational product administration and the adverse event (serious or not). "A reasonable possibility" is proposed to define cases in which there are facts/proof or arguments suggesting a causal relation, more than a relation that cannot be excluded. The investigator will use his or her clinical judgment to determine the relation. Alternative causes, such as the natural history of underlying diseases, concomitant treatment, other risk factors and the temporal relation between the event and the investigational drug will be considered and investigated. The investigator will also consult the investigator's brochure/summary of product characteristics in making the evaluation.

There may be situations in which a SAE occurs and the investigator has only minimal information to include in the initial report to the Sponsor. Nevertheless, it is very important that the investigator evaluate the causality of each event before the initial transmission of data to the Sponsor. The investigator can change his or her opinion about causality based on the information that appears during follow-up, which is why the SAE report may have to be modified. The evaluation of causality is one of the criteria that determine whether a case is compliant or not with the criteria of notification of the Health Authorities.

#### iii. Expectedness

An unexpected adverse reaction is any untoward and unintended response that is related to the administration of the study drug at any dose that is not consistent with the applicable product information (e.g., investigators brochure for an unauthorized investigational medicinal product or summary of product characteristics for an authorized product).

CRO/Sponsor will classify an Adverse Reaction as expected or unexpected according to the Reference Safety Information collected in investigator brochure or summary of product characteristics of investigational product, as appropriate. The Reference Safety Information is considered “expected” for regulatory reporting purposes by the Sponsor.

#### iv. Severity

The severity of any AEs will be graded using the CTCAE vs 5.0 (see Annex 4). If the CTCAE has no code that matches, the following guide should be used:

| Grade | Description |
|---|---|
| 0 | No adverse event |
| 1 | Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only |
| 2 | Moderate; minimal, local or non-invasive intervention indicated |
| 3 | Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated |
| 4 | Life-threatening consequences; urgent intervention indicated |
| 5 | Death related to adverse event |

Grading of AEs is based on specific clinical criteria that will require evaluation by the study site Investigator. Should an AE stop and then restart, it will be considered two separate events and the severity assessed as described above.

#### v. Additional considerations

Alterations in laboratory parameters (haematology, biochemistry or urine analysis), as well as anomalous results of other studies (such as ECGs, radiology, measurements of vital constants), including those that deteriorate in relation to baseline, should be recorded as AEs or SAEs if, in the medical and scientific opinion of the investigator, they are clinically relevant.

On the contrary, clinically significant alterations in safety parameters that are associated with the study disease are not characterized as AEs or SAEs unless the investigator thinks that they are more serious than would be expected considering the state of the patient.

Lack of efficacy is a disease-related event and should not be classified as a SAE.

Since, according to patient profile and current clinical practice, the starting dose of romiplostim will be 3 mcg/kg instead of 1 mcg/kg as indicated in the label, close monitoring of potential safety concerns will be conducted.

### c. Reporting procedures

#### i. Reporting of adverse events (AEs)

The investigator will try to obtain information about any adverse events that have occurred in all visits by examining or directly interrogating the patient.

All information referring to adverse events must be recorded in the respective section of the CRF. AEs should be recorded according CTCAE v 5.0. All adverse events that occur during the period comprehended from the time of enrolment of the patient in the study (signing of the consent form) to 30 days after last dose of the investigational products will

be recorded. When one or more signs or symptoms correspond to a disease, the main diagnosis or syndrome will be notified. All adverse events will be followed until resolution or stabilization, or until it is determined that the study treatment or the patient's participation in the study has not been the cause. All adverse events still present at the end of the study period will be monitored until their final outcome is determined.

### ii. Reporting of serious adverse events (SAEs)

All serious adverse events that occur during the clinical trial, whether or not they are related to the study drug, must be communicated immediately by e-mail or by fax within 24 h of receiving knowledge of the same or, at the latest, on the next working day at:

Unidad de Investigación Clínica y Ensayos Clínicos
Hospital Universitario Virgen del Rocío
Dpto. Farmacovigilancia
Email: pv.uicec.fisevi@juntadeandalucia.es
Avda. Manuel Siurot S/N
41013 Sevilla
Tel.: +34 955 01 34 14
Fax: +34 955095338

The investigator will collect information about the SAE on the respective form. At least these **four elements are mandatory** always to report any adverse event:

- Name or any identifier of a **reporter**
- **Subject** ID number
- At least one **suspect drug**: current dose, route, dates
- **Adverse Event** information:

    - ***Adverse Event Term Seriousness Criteria***
    - ***Adverse event outcome***
    - ***Causality assessment***

### iii. Expectedness

| IMP | RSI to be used for expectedness assessment | Relevant section to be used for expectedness assessment |
|---|---|---|
| Romiplostim | Amgen Romiplostim SPC<br>Amgen Romiplostim IB | Section 4.8<br>Section 7.6 |
| Dexamethasone | TAD Pharma Dexamethasone SPC | Section 4.8 |

### iv. Reporting of serious adverse events (SAEs) to Health Authorities

The sponsor is responsible for notifying to the Health Authorities of all suspected serious adverse reactions and unexpected, which occurred in the clinical trial. This communication shall be made within the time limits established by current legislation.

### v. Follow-up of AEs and SAEs

After the initial notification of an AE or SAE, the investigator is required to follow up each case and obtain more data on the patient's state. All the AEs and SAEs documented in previous visits must be reviewed in subsequent visits. All AEs and SAEs must be monitored until their resolution. This is applicable to all the patients, including those who withdraw early.

The investigator will include in the follow-up any additional research that may clarify the nature and/or causality of the AE or SAE. This might include additional laboratory tests or studies, histopathologic examinations, or the consultation of other healthcare professionals. Any co-investigator can ask the investigator to carry out additional evaluations to definitively clarify the nature and/or the causality of AEs or SAEs. If the patient dies while participating in the study or during a follow-up period agreed upon mutually, the investigator will provide a copy of any post-mortem finding requested, including histopathology.

### vi. AEs or SAEs that occur after the study ends

Post-study AEs or SAEs are defined as any event that occurs outside the Follow-up period of detection defined in the protocol. The investigator is not required to actively seek out AEs or SAEs in patients who have participated in the clinical trial in the past. Nevertheless, if the investigator comes to know of the existence of any AE or SAE, including the death of the patient at any time after a patient has left the study, and this AE or SAE is considered related to the study drug, the investigator must notify the sponsor promptly.

### vii. Adverse Events of special interest (AESIs)

An AESI is an adverse event of scientific and medical concern specific to the study treatment in order to obtain a greater knowledge about its safety profile. The AESIs can be severe or not.

Any AE (serious or non-serious) that is of scientific and medical concern specific to the study treatment, for which ongoing monitoring and rapid communication by the Investigator to SPONSOR. Early notification allows a continuous monitoring of these events in order to be characterized and understood in relation with the use of study drug.

Adverse Events of Special Interest (AESIs) for romiplostim are the following:

- Haemorrhage
- Thrombotic/thromboembolic events
- Progressing existing myelodysplastic syndrome (MDS)
- Neutralizing antibodies that cross react with eTPO

- Haemolytic anaemia
- Interstitial lung disease and pulmonary fibrosis
- Non-haematological malignancies

When the patient begins the treatment with romiplostim, any event that is categorized as a romiplostim AESI, would need to be reported as AESI even if it is non-serious. AESI notification is irrespective of the severity/grade of event and relationship to romiplostim.

### viii. Timeframes for Submission of Safety Data to Amgen

Regarding the timeframes for submission of Safety Data to Amgen the information of the next tables must be followed (Table 4 and Table 5).

**Table 4. For interventional studies with Amgen IMPa**

| Safety Data | Timeframe for submission to Amgen | Send to |
|---|---|---|
| Suspected Unexpected Serious Adverse Reaction (SUSARs) | At time of regulatory submission | Amgen Safety |
| Pregnancy/Lactation exposure and any associated reports/outcomes (i.e. unexpected pregnancy, pregnancy of partner, spontaneous abortion, congenital anomaly etc.) | Within 1 business day of Sponsor awareness, for reports meeting serious criteria<br>Not to exceed 15 calendar days of Sponsor awareness, for non-serious reports | Amgen Safety |

[a] Specific requirements are to be outlined in the Research Agreement.

**Table 5. Adverse Device Effects for Amgen-marketed devices and device constituents in combination products[b,c] and Product complaints:**

| Safety Data | Timeframe for submission to Amgen | Send to |
|---|---|---|
| Unanticipated Serious Adverse Device Effects, (USADEs), Serious Adverse Device Effects (SADEs) and Non-serious Adverse Device Effect (Non-serious ADEs) | Within 1 business day of Sponsor awareness | Amgen Safety |
| Product Complaints[c] | Within 1 business day of Sponsor awareness | Amgen Quality |

Specific requirements are to be outlined in the Research Agreement. Requirements in the table should ALWAYS be included, regardless if the Amgen device/combination product is being studied used in the study or if the device/combination product is used as standard of care in the study.

[a]Amgen combination products and devices that are marketed anywhere in the world (regardless of the status of the combination product/device in the country where the study is carried out).

[b] Adverse device effect (ADE) is any adverse effect caused by or associated with the use of a device constituent of a combination product or medical device. Adverse device effects include, but are not limited to, adverse effects resulting from insufficient or inadequate instructions for use, any malfunction of the device, or use error or intentional misuse of the device.

Unanticipated serious adverse device effect (USADE).

- ISO14155/MEDDEV2.7.3 definition: Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report
    - Note: The 'risk analysis report' refers to the most current risk documents for a given investigational device. The essence of the risk documents is captured under the Risk Assessment section of the device IB or the device section of a combination product IB.

- US FDA definition (Unanticipated adverse device effect (UADE)): Any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

[c]Product Complaint is: Any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug, combination product, or device after it is released for distribution to market or clinic by either: (1) Amgen or (2) distributors or partners for whom Amgen manufactures the material. This includes all components distributed with the drug, such as packaging, drug containers, delivery system, labelling, and inserts. Examples include:

- Device that is damaged or broken
- Bent or blunt needles
- Missing or illegible labeling
- Inability of customer to administer the product
- Product with an unexpected color, appearance, or particles
- Use error (i.e., an act or omission of an act that results in a different combination product or medical device response than intended by the manufacturer or expected by the user, where the user attempted to use the combination product or medical device in good faith and experienced difficulty or deficiency administering the product).

Reports of misuse of a combination product or medical device (i.e., the intentional and improper use of a combination product or medical device not in accordance with the authorized product information) are not considered Product Complaints.

**Table 6. Aggregate reports[a] (For all study types, as applicable):**

| Safety Data | Timeframe for submission to Amgen | Send to |
|---|---|---|
| Listing for Safety data reconciliation[b] | Once per year and at the end of the study | NASCR Manager |
| Annual Safety Report (e.g., EU Clinical Trial Directive DSUR and US IND Annual Report) | Annually | NASCR Manager |
| Other aggregate analyses (any report containing Safety data generated during the course of the study) | At the time of Sponsor submission to anybody governing research conduct (e.g. RA, IRB etc.) | NASCR Manager |
| Final (End of Study Report, including):<br>• Unblinding data for blinded studies<br>• Reports of unauthorized use of a marketed product | At the time of Sponsor submission to anybody governing research conduct (e.g. RA, IRB etc.) but no later than 1 calendar year of study completion | NASCR Manager |

[a] Specific requirements are to be outlined in the Research Agreement.

[b] Listing for reconciliation should include all ICSRs submitted to Amgen Safety per contract (for studies in Table 2 listing should contain SUSARs, pregnancy and lactation exposure (and any associated reports/outcomes), USADEs, SADEs and non-serious ADEs).

# 11. STATISTICAL CONSIDERATIONS

### a. General considerations

The statistical analysis plan will be developed and finalized before database lock.

Descriptive statistics will be obtained for all variables: mean, median, standard deviation and range, Q1, Q3, and CI 95% for continuous variables, and frequencies and percentages for categorical variables.

Summary statistics will be provided by treatment groups for disposition, demographics, baseline characteristics, exposure to investigational product, adverse events, concomitant medication, labs and clinical outcome assessment data.

A Chi- square test or Fisher test if applicable will be used to compare categorical variables between groups. Time-to-event variables will be estimated by the Kaplan-Meier method from the randomisation. The log-rank test will be used to compare the survival curves. All the other endpoints will be compared between the two arms with appropriate statistical tests. All statistical tests will be two-sided with an α-level of 0.05.

### b. Sample size

The primary endpoint of this study is the 6mSROT-50 ($\geq 50 \times 10^9$/L) rate at 6 months from treatment cessation. In patients with newly diagnosed primary immune thrombocytopenia

treated with dexamethasone 40 daily x 4 days for one to three cycles, 6mSROT-50 (≥50x$10^9$/L) at 6 months from treatment cessation has been assumed to be 30% [2]. The sample size was based on the assumption that ROM + DEX can improve sustained response at 6 months from treatment cessation up to 56.6% similarly to eltrombopag plus dexamethasone as described by Zhang [2]. A total of 63 patients/arm are required to achieve 80% power to detect a difference with a two-sided significance level of 5%, if the true 6mSROT-50 rates at 6 months from treatment cessation are 30% in the DEX arm and 56,6% in the ROM + DEX arm and assuming a dropout rate of 15%. The total minimal size is 126 patients to be randomized.

### c. Analytical Populations

**Safety Population**

The safety population will consist of all randomized subjects who received at least one dose of study treatment. Subjects will be analysed according to the treatment actually received. Analysis for safety endpoints will use this analysis set.

**ITT Population**

All patients who are randomized will be included in the ITT Population. The ITT Population will be used to summarize subject disposition and baseline characteristics. Patients will be analysed according to the treatment they were allocated to at randomization; not necessarily the treatment they actually received. Results will be presented “as randomized.”

**mITT Population**

All patients who are randomized and received at least one dose of study medication will be included in the mITT Population. The mITT Population is the primary analysis population for efficacy. Patients will be analysed according to the treatment they were allocated to at randomization; not necessarily the treatment they actually received. Results will be presented “as randomized.”

**rITT Population**

All patients who are randomized and received at least one dose of study medication and achieved response (R) at any time during the study will be included in the rITT Population. The rITT Population will be used for the analysis of time to loss of response. Patients will be analysed according to the treatment they were allocated to at randomization; not necessarily the treatment they actually received. Results will be presented “as randomized.”

### d. Analysis of Primary Objective

The primary endpoint is 6mSROT-50 rate at 6 months (180 days) from treatment cessation.

The proportion of patients with 6mSROT-50 and corresponding 95% CIs for each study arm will be provided. A Chi-square test or Fisher test if applicable, will be used to compare the proportion of 6mSROT-50 between treatment arms.

### e. Analysis of Secondary Objectives

#### i. Secondary Efficacy evaluations

For the analysis of the secondary endpoints, following analyses will be conducted:

- The proportion of patients with 6mSROT-30, 12mSROT-30 and 12mSROT-50 and corresponding 95% CIs for each study arm will be provided. A Chi-square test or Fisher test if applicable will be used to compare the proportion of each endpoint between treatment arms.
- The proportion of patients with CR, R, GR or TR at 6 and 12 and *End of study Visit (visit 12 months after the last dose of study treatment)*will be calculated and corresponding 95% CIs for each study arm will be provided. A Chi-square test or Fisher test if applicable will be used to compare the proportion of each endpoint between treatment arms.
- To compare the time to first response (R) in both arms, Kaplan-Meier method will be used. Patients who not achieve R will be censored at the date of the last follow-up. Median and 95% CI, number of events and censored and risk number of patients will be provided. Log rank test will be used to compare time to first response between treatment arms. We will evaluate this in the total sample and in the absence of any rescue treatment.
- The proportion of patients with ER at Day 7 and IR at Day 30 from randomisation will be calculated and corresponding 95% CIs for each study arm will be provided. A Chi- square test or Fisher test if applicable will be used to compare the proportion of each endpoint between treatment arms.
- Descriptive statistics (mean, median, standard deviation, min, max, Q1 and Q3) and Student's t test will be used to compare the duration of platelet response through the following endpoints:
    - maximum number of consecutive days with platelet response (CR, R, GR and TR) along the study period and,
    - total number of days with platelet response (CR, R, GR and TR) along the study period in both arms. We will evaluate them in the total sample and in the absence of any rescue treatment.
- To compare the time to loss of response (LoR) in the subgroup of patients who achieve R (rITT population) between both arms, Kaplan-Meier method will be used. Patients who do not achieve LoR will be censored at the date of the last follow-up. Median and 95% CI, number of events and censored and risk number of patients will be provided. Log rank test will be used to compare time to first response between treatment arms.

- The proportion of patients requiring any rescue treatment along the study period will be calculated and corresponding 95% CIs for each study arm will be provided. A Chi-square test or Fisher test if applicable, will be used to compare the proportion between treatment arms.

Frequency and proportion of patients with adverse events, including bleeding events measured by the WHO bleeding scale will be provided. A Chi-square test or Fisher test if applicable will be used to compare the proportion between treatment arms.

- Quality of life measures using the SF-36 v2, FACIT-F and ITP-PAQ will be analysed. Change from baseline Day 1, (the day of administration of the first dose of study medication) to Week 8, Month6 (Day 180), Month12 (Day 365) and End of study Visit (visit 12 months after the last dose of study treatment) of SF-36 v2, FACIT-F and ITP-PAQ total score and each dimension score of SF-36 v2, FACIT-F and ITP-PAQ will be calculated. Both the change of scores and the scores at every assessed time point will be reported using the mean, median, standard deviation, min, max, Q1 and Q3.Student's t test will be used to compare the scores between treatment arms at different time points. Paired Student's t test will be used to evaluate the change from baseline at different time points within each treatment arm.
- The sum of all worst grades within each domain from the ITP-BAT questionnaire will be calculated and described at every assessed time point using the mean, median, standard deviation, min, max, Q1 and Q3.Student's t test will be used to compare the scores between treatment arms at different time points. Also, the change from baseline to Day 1, Week 8, Week 12, Month6 (Day 180), Month12 (Day 365) and End of study Visit (visit 12 months after the last dose of study treatment) of the sum of all worst grades within each domain from the ITP-BAT questionnaire will be calculated and described at every assessed time point using the mean, median, standard deviation, min, max, Q1 and Q3. Paired Student's t test will be used to evaluate the change from baseline at different time points within each treatment arm.
- Health resources use (HRU) associated with the ITP from treatment initiation (outpatient visits and home health care, hospitalizations and emergency visits, diagnostic procedures, pharmacological and non-pharmacological treatments and HRU related to of adverse drug reactions) and loss of productivity (number of days of absenteeism from school or work) will be summed up along the study and described using the mean, median, standard deviation, min, max, Q1 and Q3. Student's t test will be used to compare the scores between treatments.

  In all hypothesis testing, $p<0.05$ will be considered statistically significant. No adjustments for multiplicity will be done. Since the amount of analysis of secondary objectives is numerous, results of the secondary endpoints should be considered exploratory and interpreted with caution.

### ii. Secondary Safety evaluations

Safety assessment will consist of monitoring adverse events (AEs), including serious adverse events (SAEs) and laboratory safety parameters. AEs will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Bleeding events will be carefully monitored. AE terms will be coded using MedDRA (lastest version). The description of number and percentage of patients with each adverse event ordered by SOC/PT by grade and total will be summarized descriptively by treatment group.

The number of patients experiencing AEs and number of AEs will be summarized by treatment group using frequency counts.

## 12. DATA HANDLING AND QUALITY ASSURANCE

### a. Monitoring of the trial

The clinical monitors are employees of the CRO, and representatives of the sponsor. As such, they have the obligation to follow the trial closely so that all aspects of the trial are carefully monitored for compliance with applicable government regulations and with ICH E6 (R2) guidelines.

The clinical monitors will visit the study sites and Investigators at intervals as defined in the monitoring plan, in addition to maintaining necessary contact through telephone, e-mail, and letter. The clinical monitors will maintain current personal knowledge of the trial through observation, review of trial records and source documentation, and discussion of the conduct of the trial with the study site Investigators and staff.

### b. Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) comprised of 3 blinded clinical haematologists (not part of the study as investigators) with extensive clinical research experience will assess treatment outcomes to protect the safety and interests of trial participants.

The members, frequency and methods of meeting, as well as the issues to be reviewed will be specified in the DSMB Charter. The DSMB will also meet in the event of any new safety information that is essential to the study. The DSMB procedures and functions will be guided by international recommendations for these committees.

The DSMB chairperson will be responsible for providing a written report of findings and recommendations to the study sponsor. The study sponsor will be responsible for informing sites and regulatory authorities of any DSMB recommendations regarding the conduct of the study.

If the sponsor decides not to follow the recommendations provided by the DSMB, the sponsor will inform the IRB/IEC with a justification as to why the recommendations have not been followed.

### c. Audits

The sponsor may choose to schedule and conduct periodic audits of ongoing clinical studies. Audits are independent of, and separate from, routine monitoring or quality control functions and are conducted to assure accuracy and compliance with the protocol, governing regulatory authorities and/or ICH E6 (R2) guidelines.

### d. Reporting of serious breaches

Serious breaches of the authorized protocol or of the Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16th April 2014 on clinical trials on medicinal products for human use and / or local regulations occurring in each country must be reported by the sponsor without undue delay and no later than seven calendar days from becoming aware of the breach to the National Regulatory Authority and the IEC.

To this end, a serious breach shall be defined as a breach that may significantly affect the safety and rights of the trial subjects or the reliability and robustness of the data generated in the clinical trial.

National Regulatory Authority of different countries and the applicable IEC, and the breaches that do not constitute a serious breach should not be notified.

Each study site Investigator must document and explain in the subject's source documentation any breaches from the approved protocol and / or the Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16th April 2014 on clinical trials on medicinal products for human use and / or local regulations. Investigators may implement a breach to eliminate an immediate hazard to trial subjects without prior IEC informed consent approval, but the breach must be reported to the monitor/CRA within 1 working day. Such incidents will be evaluated for potential safety hazards of the ongoing study, and if deemed appropriate, a protocol amendment will be issued.

The monitor/CRA will document breaches throughout the course of monitoring visits. The monitor will notify the Investigator during a visit and a "Breach Form" will be completed and signed by the investigator and by the monitor.

### e. Data Management

CRO will be responsible for processing and quality control of the data. Data will be handled in accordance with the Data Management Plan, Standard Operating Procedures and applicable regulatory guidelines.

Data management based on GCP refers to activities defined to achieve safe routines for efficient entry of subject information into a database, avoiding errors. The routines include procedures for handling of eCRFs, database set-up and management, data entry and verification, data validation, quality control (QC) of database, and documentation of the performed activities, including information of discrepancies in the process. The

database, the data entry screens and the program, will be designed in accordance with the clinical study protocol by CRO.

### f. Electronic Case Report Forms (eCRFs)

Data collection for this study will consist of electronic data capture for all eCRF information. CRO will supply the eCRF.

All study site Investigators agree to maintain accurate eCRFs and source documentation as part of the case histories.

All information is to be filled in the subject's eCRF. If an enrolled subject is not randomized into the study (i.e., fails screening), only minimum data (such as demographics and consent date) and the reason for failing screening should be reported on the eCRF. In general, no queries for missing data on these subjects will be issued for procedures indicated as 'Not done'.

For randomized subjects, information captured on the source documents will be entered into the subject's eCRF by study site personnel and monitored at the study site. If an item is not available or is not applicable, this fact should be indicated by a missing reason. Blank spaces should not be present unless otherwise directed. Any corrections should be made using the procedure outlined in the Case Report Form Completion Guide of the study manual and will be recorded in the eCRF.

Each completed eCRF must be reviewed, signed, and dated by the study site Investigator in a timely manner. The completed eCRF will be reviewed by the study Monitor as soon as practical after completion. A copy of the final, approved and signed eCRF will be provided to the site and should be stored in the appropriate files.

### g. Web-based eCRF

Clinical data (including AEs and concomitant medications) will be entered into an Electronic Data Capture (EDC) application. The data system is password protected and includes internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete or inaccurate. Clinical data will be entered directly from the source documents. Roles and rights of the study site personnel responsible for entering the study data into the eCRF will be determined in advance. Only authorized study site personnel designated by each study site Investigator will complete data collection. Appropriate training and security measures will be completed with the Investigator and all authorized study site personnel, prior to the study initiation, and before any study data is entered into the system.

### h. Entering of Data into the eCRF

All data must be entered in English. The eCRFs should always reflect the latest observations on the subjects participating in the study. Therefore, the eCRFs should be completed as soon as possible during or after the subject's visit. Each study site Investigator must verify that all data entries in the eCRFs are accurate and correct.

If some assessments are not done, or if certain information is not available, not applicable or unknown, the Investigator or authorized designee should indicate this in the eCRF. The investigator will approve the data using an electronic signature, and this approval is used to confirm the accuracy of the data recorded.

### i. The Query Process

Each monitor will review the eCRFs and evaluate them for completeness and consistency. Each eCRF will be compared with the respective source documents to ensure that there are no discrepancies between critical data. All entries, corrections and alterations are to be made by the Investigator or his/her authorized designee. The monitor cannot enter data in the eCRFs.

Once clinical data of the eCRF have been submitted to the central server, corrections to the data fields will be audit trailed (i.e., the reason for any change, the name of the person who performed the change, and time and date will be logged).If additional corrections are needed, the responsible monitor or Data Manager will raise a query in the EDC application. The appropriate investigational staff will answer queries generated in the application. This process is audit trailed meaning that the name of investigational staff, time, and date is logged.

### j. Source Documents

The eCRF is essentially considered a data entry form and should not constitute the original (or source) medical records unless otherwise specified. Source documents are all documents used by the Investigator or hospital that relate to the subject's medical history, that verify the existence of the subject, the inclusion and exclusion criteria, and all records covering the subject's participation in the study. They include enrolment and randomization log, investigational product accountability log, laboratory notes, memoranda, material dispensing records, subject files, etc.

Each Investigator is responsible for maintaining source documents. These will be made available for inspection by the study monitor at each monitoring visit. All supportive documentation submitted with the eCRF, such as laboratory data should be clearly identified with the study, visit and subject number. Any personal information (e.g., subject name, initials) should be removed or rendered illegible to preserve individual confidentiality.

### k. User ID

eCRF records will be automatically appended with the identification of the creator, by means of their unique User ID. Specified records will be electronically signed by the Investigator to document his/her review of the data and acknowledgement that the data are accurate. This will be facilitated by means of the Investigator's unique User ID and password; date and time stamps will be added automatically at time of electronic signature. If an entry in an eCRF requires change, the correction should be made in accordance with the relevant software procedures.

### l. Audit Trail

To meet regulatory requirements, the eCRF data will be electronically stored at sites. All changes will be fully recorded in a protected audit trail, and a reason for the change will be required. Once all data have been entered, verified, and validated, the database will be locked to prevent any further changes in the clinical study data.

### m. Inspection of Records

The Investigators and institutions involved in the trial will permit trial-related monitoring, audits, IEC review, and regulatory inspection(s) by providing direct access to all trial records. In the event of an audit, the Investigator agrees to allow the sponsor, representatives of the sponsor, and the governing regulatory agency access to all trial records.

The Investigator should promptly notify the sponsor of any inspections scheduled by any regulatory authorities and promptly forward copies of any inspection reports received to the sponsor.

### n. Trial Record Retention

Essential documents and eCRF data should be retained during25 years.

## 13. ADMINISTRATIVE CONSIDERATIONS

The following administrative items are meant to guide each study site Investigator in the conduct of the study but may be subject to change based on industry and government SOPs or working practice documents or guidelines.

### a. Legal Considerations

The current clinical trial will be conducted in accordance with the protocol, the principles established in the current revised version of the Declaration of Helsinki (Annex 1) and the applicable regulatory requirements, particularly the ICH Tripartite Harmonized Guidelines for good clinical practice (1996), the Regulation (EU) 536/2014 relative to clinical trials on medicinal products for human use and the locally applicable regulations.

### *b.* Regulatory authority approvals/authorizations

The present study will be carried out in accordance with the provisions of RD 1090/2015 of December 4, which regulates clinical trials with medications, the Ethics Committees for Research with Medicines and the Spanish Registry of Clinical Studies; Royal Legislative Decree 1/2015, of July 24 Law on guarantees and rational use of medicines and health products; Royal Decree 577/2013 of July 26, which regulates drug surveillance, and the Law 14/2007 of July 3, Biomedical Research, all of them as applicable, as well as the Declaration of Helsinki and the guidelines of good clinical practice and recommendations of the ICH.).

The study protocol, the patient information sheet + informed consent form and other relevant documents related to the study must be sent to the chosen CEIm and other relevant documents related to the study in order to obtain approval according to current regulations, before starting the inclusion of patients. Also, all the monitoring requirements during the study as annual reporting obligations will be done following the regulatory specifications.

In addition, the guidelines on good pharmacovigilance practices (GVP module VI will be followed) [47].

### c. Ethics committee review

ICH guidelines require that approval be obtained from Health Authorities and an Ethics Committee before human subjects can participate in research studies. Prior to the trial onset, the protocol, informed consent, advertisements to be used for subject recruitment (if applicable), and any other written information regarding this trial to be provided to the subject will be approved by the Ethics Committee. The clinical study will only be started when both the Health Authorities and an Ethics Committee have considered that the expected benefits for the trial subject and society justify the risks; in addition, the trial will only be continued if compliance with this criterion is constantly supervised.

CRO will obtain Ethics Committee approvals on behalf of the sponsor and investigators. All regulatory approvals should be signed by the Ethics Committee Chairman or designee and must identify the Ethics Committee name and address, the clinical protocol by title and/or protocol number and the date approval and/or favorable opinion was granted. Documentation of all Health Authorities and Ethics Committee approvals and of the Ethics Committee compliance with ICH E6(2) will be maintained by the site and will be available for review.

### d. Modifications of the protocol

Any change in the approved protocol will require a Protocol amendment. The Investigator must not make any change in the study without favourable opinion from the Ethics Committee and authorization from the Health Authorities, except as necessary to eliminate an impending and obvious risk for the subjects except when necessary to remove an apparent, immediate hazard to subjects. Protocol changes introduced to eliminate an impending and obvious risk may be implemented immediately, but must subsequently be documented in an amendment, reported to the Ethics Committee and be submitted to the relevant Health Authorities within the required timeframe.

Any substantial amendments to the protocol must be submitted in writing to the Ethics Committee and the Health Authorities for approval before the changes proposed in the amendment are implemented. Depending on the magnitude of the change, the recruitment may be temporally halted.

The sponsor does not have to notify non-substantial amendments to the Health Authorities or the Ethics Committee. However, any non-substantial amendments will be

recorded and contained in the documentation when it is subsequently submitted, for example in the subsequent notification of a substantial amendment. Documentation of any non-substantial amendments will be available on request for inspection at the trial site or the sponsor premises as appropriate.

### e. Informed consent

A written informed consent in compliance with ICH E6 guidelines shall be obtained from each subject before being included in the study or performing any study specific procedures.

In obtaining and documenting informed consent, the Investigator should comply with the applicable regulatory requirements, and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. The consent form and any revision(s) should be approved by the Ethics Committee prior to being provided to potential subjects.

The written Informed Consent Form (ICF) should be prepared in the local language(s) of the potential subject population.

An approved informed consent form will be provided by the sponsor to investigative site.

Before a subject's participation in the study, it is the Principal Investigator's (or their designee) responsibility to obtain freely given consent in writing, from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential risks of the study and before any protocol-specific screening procedures or any study drugs are administered. Subjects must have the opportunity to ask questions and receive answers and will have adequate time to decide whether or not to participate in the study. Once the Investigator is assured that the subject understands the implications of participating in the trial, the subject will be asked to give consent to participate in the trial by signing the informed consent.

The ICF should be signed and personally dated by the subject and by the physician who conducted the informed consent discussion (Principal Investigator or designee). The subject's written informed consent should also be documented in the subject's medical records.

The Investigator shall provide a copy of the signed informed consent to the subject. A second original form shall be maintained in the Investigator study file at the site.

If the informed consent is revised during the course of the trial, all active participating subjects must sign the revised form approved by the Ethics Committee.

The subject participating in a clinical trial, or his/her legal representative, may withdraw consent at any time without giving any reason and without this involving any penalty or prejudice for the participating subject.

### f. Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. Each Investigator will ensure that all site personnel involved will respect the confidentiality of any information about trial subjects. Management of personal data from subjects participating in the trial, particularly as regards consent, will comply with Regulation (EU) 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 local laws.

At each site, all records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject. Subject identity is confidential and may only be known by the Investigator, trial personnel, appointed auditors and monitors, and Health Authorities.

Each Investigator and all employees and coworkers involved with this trial may not disclose or use for any purpose other than performance of the trial, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the trial. Prior written agreement from the sponsor or its designee must be collected for the disclosure of any said confidential information to other parties.

### g. Insurance

The sponsor has contracted an insurance policy to cover the responsibilities of the investigator and other parties participating in the study, according to the applicable legislation.

- Insurance company: HDI Global SE España
- Policy Number: 08057795-30068

### h. Publications

The sponsor commits to responsible publication of both the positive and negative results from its clinical trials as required by all governing regulatory and health authorities.

Investigators will not publish the global study results (all sites) unless the sponsor has not done so in a suitable time period after the clinical study report (CSR) has been available. Should the Investigator(s) independently seek to publish results of this study which occur at their study site(s), they must inform the study sponsor of any/all drafts (including, but not limited to papers, manuscripts or abstracts) at least 60 days before submission to the congress, meeting or journal. The sponsor and Investigator(s) will agree with all aspects related to any proposed publications with regards to the following:1) any proposed publications will be drafted in agreement with international recommendations, such as those from the International Committee of Medical Journal Editors (ICMJE) and all elements of the Consort Statement (2010), to maintain integrity of the trial results in all communications; 2) any proposed publications will state the Clinical Research Ethics Committees which approved the trial and the funding sources

of the trial; 3) any proposed publications will occur before disclosure of results to lay people; 4) any proposed publications will not report premature or partial data prior to completion of the analysis of the overall results of the trial.

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# Annex 1. Declaration of Helsinki

# WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964

and amended by the:

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996

52nd WMA General Assembly, Edinburgh, Scotland, October 2000

53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)

55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)

59th WMA General Assembly, Seoul, Republic of Korea, October 2008

64th WMA General Assembly, Fortaleza, Brazil, October 2013

**Preamble**

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

**General Principles**

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or

other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

**Risks, Burdens and Benefits**

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

**Vulnerable Groups and Individuals**

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

**Scientific Requirements and Research Protocols**

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and

information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

**Research Ethics Committees**

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

**Privacy and Confidentiality**

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

**Informed Consent**

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent

have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

**Use of Placebo**

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

**Post-Trial Provisions**

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

**Research Registration and Publication and Dissemination of Results**

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

**Unproven Interventions in Clinical Practice**

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

## Annex 2. List of Sites / Principal Investigators

Attached as a separate document.

## Annex 3. Informed Consent Form

Attached as a separate document.

## Annex 4. NCI-CTC AE Criteria

Common terminology criteria for classification of adverse events version 5.0 (NCI CTC AEv5.0) are available at the following Internet address:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

## Annex 5. Contraceptive Guidance and Collection of Pregnancy and Lactation Information

Female subjects of childbearing potential must receive pregnancy prevention counseling and be advised of the risk to the fetus if they become pregnant during treatment and for 30 days after the last dose of protocol-required therapies.

Additional medications given during the study may alter the contraceptive requirements.

These additional medications may require female subjects to use highly effective methods of contraception and for an increased length of time. In addition, male subjects may also be required to use contraception. The investigator must discuss these contraceptive changes with the subject.

### Definition of Females of Childbearing Potential

A female is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Females in the following categories are not considered female of childbearing potential:

- Premenopausal female with 1 of the following:
    - Documented hysterectomy;
    - Documented bilateral salpingectomy; or
    - Documented bilateral oophorectomy.

Note: Site personnel documentation from the following sources is acceptable:

1) review of subject's medical records;

2) subject's medical examination; or
3) subject's medical history interview.

- Premenarchal female
- Postmenopausal female:
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
    - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment

**Contraception Methods for Female Subjects**

Acceptable Methods of Effective Contraception:

- Combined (estrogen and progestogen containing) or progestogen-only hormonal methods given via oral, intravaginal, transdermal, injectable, or implantable route)
- Intrauterine device (IUD)
- Intrauterine hormonal-releasing system (IUS)
- Bilateral tubal ligation/occlusion
- Vasectomized partner (provided that partner is the sole sexual partner of the female subject of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success)
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments; the reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject)
- Male or female condom with or without spermicide
- Cap, diaphragm or sponge with spermicide
- Double barrier method: the male uses a condom and the female may choose either a cap, diaphragm, or sponge with spermicide (a female condom is not an option due to the risk of tearing when both partners use a condom)

Unacceptable Methods of Birth Control for Female Subjects

Birth control methods that are considered unacceptable in clinical trials include:

- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus)
- Spermicides only

- Lactational amenorrhoea method

**Collection of Pregnancy Information**

Female Subjects Who Become Pregnant

- Investigator will collect pregnancy information on any female subject who becomes pregnant while taking protocol-required therapies through 30 days after last dose of IP.
- Information will be recorded on the Pregnancy Notification Worksheet. The worksheet must be submitted to sponsor within 24 hours of learning of a subject's pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Worksheet that violates the country or regions local privacy laws.)
- After obtaining the female subject's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant while taking protocol-required therapies through 30 days of last dose of the study drug. This information will be forwarded to Sponsor. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of pregnancy will be reported to Sponsor, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or report of a congenital anomaly or developmental delay, fetal death, or suspected adverse reactions in the neonate will be reported as an adverse event or serious adverse event. Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an adverse event, but still must be reported to Amgen as a pregnancy exposure case.
- If the outcome of the pregnancy meets a criterion for immediate classification as a serious adverse event (e.g., female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the investigator will report the event as a serious adverse event.
- Any serious adverse event occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to Sponsor as described in Appendix 4. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of a serious adverse event through spontaneous reporting.
- Any female subject who becomes pregnant while participating will discontinue study treatment.

Male Subjects With Partners Who Become Pregnant or Were Pregnant at the Time of Enrollment

- In the event a male subject fathers a child during treatment, and for an additional 30 days after discontinuing protocol-required therapies, the information will be recorded on the Pregnancy Notification Worksheet. The worksheet must be submitted to Sponsor within 24 hours of the site's awareness of the pregnancy.
- The investigator will attempt to obtain a signed authorization for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.
- After obtaining the female partner's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Sponsor.
- Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of the pregnancy will be reported to Sponsor regardless of fetal status (presence or absence of anomalies) or indication for procedure.

**Collection of Lactation Information**

- Investigator will collect lactation information on any female subject who breastfeeds while taking protocol-required therapies through 30 days after last dose of IP.
- Information will be recorded on the Lactation Notification Worksheet and submitted to Sponsor within 24 hours of the investigator's knowledge of event.
- Study treatment will be discontinued if female subject breastfeeds during the study.
- With the female subjects signed authorization for release of mother and infant health information, the investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking protocol- -required therapies through 30 days after discontinuing protocol-required therapies.

## Annex 6. Hepatotoxicity Stopping Rules: Suggested Actions and Follow-up Assessments and Study Treatment Rechallenge Guidelines

Subjects with abnormal hepatic laboratory values (i.e., alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin [TBL]) and/or international normalized ratio (INR) and/or signs/symptoms of hepatitis (as described below) may meet the criteria for withholding or permanent discontinuation of study therapies, as specified in the *Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009*.

### Criteria for Withholding and/or Permanent Discontinuation of Protocol-required Therapies Due to Potential Hepatotoxicity

The following stopping and/or withholding rules apply to subjects for whom another cause of their changes in liver biomarkers (TBL, INR and transaminases) has not been identified.

Important alternative causes for elevated AST/ALT and/or TBL values include, but are not limited to:

- Hepatobiliary tract disease
- Viral hepatitis (e.g., hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, herpes simplex virus, varicella, toxoplasmosis, and parvovirus)
- Right sided heart failure, hypotension or any cause of hypoxia to the liver causing ischemia
- Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants and mushrooms
- Heritable disorders causing impaired glucuronidation (e.g., Gilbert's syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (e.g., indinavir, atazanavir)
- Alpha-one antitrypsin deficiency
- Alcoholic hepatitis
- Autoimmune hepatitis
- Wilson's disease and hemochromatosis
- Nonalcoholic fatty liver disease including steatohepatitis (NASH)
- Non-hepatic causes (e.g., rhabdomylosis, hemolysis)

If investigational product(s) is/are withheld, the subject is to be followed for possible drug-induced liver injury (DILI) according to recommendations in the last section of this appendix.

Rechallenge may be considered if an alternative cause for impaired liver tests (ALT, AST, ALP) and/or elevated TBL, is discovered and the laboratory abnormalities resolve to normal or baseline (see next section in this appendix).

**Table 12-2. Conditions for Withholding and/or Permanent Discontinuation of Protocol-required Therapies Due to Potential Hepatotoxicity**

| Analyte | Temporary Withholding | Permanent Discontinuation |
|---|---|---|
| TBL | > 3x ULN<br>at any time | > 2x ULN |
| | | OR |
| INR | -- | > 1.5x ULN (for subjects not on anticoagulation therapy) |
| | OR | AND |
| AST/ALT | > 8x ULN at any time | In the presence of no important alternative causes for elevated AST/ALT and/or TBL values |
| | > 5x ULN but < 8x ULN for ≥ 2 weeks | |
| | > 5x ULN but < 8x ULN and unable to adhere to enhanced monitoring schedule | > 3x ULN (when baseline was < ULN) |
| | > 3x ULN with clinical signs or symptoms that are consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, and jaundice) | |
| | OR | |
| ALP | > 8x ULN at any time | -- |

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; TBL = total bilirubin; ULN = upper limit of normal.

**Criteria for Rechallenge of Protocol-required Therapies After Potential Hepatotoxicity**

The decision to rechallenge the subject is to be discussed and agreed upon unanimously by the subject, investigator, and the sponsor.

If signs or symptoms recur with recalling, then IP is to be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Table 12-2) are never to be rechallenged.

Reporting

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST or ALT and TBL and/or INR elevation, according to the criteria specified in the above, require the following:

- The event is to be reported to Sponsor as a serious adverse event within 24 hours of discovery or notification of the event (i.e., before additional etiologic investigations have been concluded)
- The appropriate CRF (e.g., Event CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to Sponsor

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event.

Additional Clinical Assessments and Observation

All subjects in whom investigational product(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in Table 12-2 or who experience AST or ALT elevations > 3 x upper limit of normal (ULN) or 2-fold increases above baseline values for subjects with elevated values before drug are to undergo a period of “close observation” until abnormalities return to normal or to the subject’s baseline levels. Assessments that are to be performed during this period include:

- Repeat AST, ALT, ALP, bilirubin (total and direct), and INR within 24 hours
- In cases of TBL > 2x ULN or INR > 1.5, retesting of liver tests, bilirubin (total and direct), and INR is to be performed every 24 hours until laboratory abnormalities improve Testing frequency of the above laboratory tests may decrease if the abnormalities stabilize or the investigational product(s) or protocol-required therapies has/have been discontinued and the subject is asymptomatic.

Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL. The following are to be considered depending on the clinical situation:

- Complete blood count (CBC) with differential to assess for eosinophilia
- Serum total immunoglobulin IgG, anti-nuclear antibody (ANA), anti smooth muscle antibody, and liver kidney microsomal antibody -1 (LKM1) to assess for autoimmune hepatitis.
- Serum acetaminophen (paracetamol) levels.
- A more detailed history of:
    - Prior and/or concurrent diseases or illness.
    - Exposure to environmental and/or industrial chemical agents.
    - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting and fever.
    - Prior and/or concurrent use of alcohol, recreational drugs and special diets.
    - Concomitant use of medications (including non-prescription medicines and herbal and dietary supplements), plants, and mushrooms.
- Viral serologies.
- Creatine phosphokinase (CPK), haptoglobin, lactate dehydrogenase (LDH), andperipheral blood smear.
- Appropriate liver imaging if clinically indicated.
- Appropriate blood sampling for pharmacokinetic analysis if this has not already been collected.
- Hepatology consult (liver biopsy may be considered in consultation with a hepatologist).

Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal or considered stable by the investigator. The “close observation period” is to continue for a minimum of 4 weeks after discontinuation of all investigational product(s) and protocol-required therapies.

The potential DILI event and additional information such as medical history, concomitant medications and laboratory results must be captured in the corresponding CRFs.