Official Title: **A PROSPECTIVE OPEN-LABEL STUDY OF THE EFFECTIVENESS OF EPOETIN BETA FOR TREATING ANEMIC PATIENTS WITH LOW/INTERMEDIATE-1-RISK MYELODYSPLASTIC SYNDROME (MDS)**

NCT Number: NCT02145026

Document Date: Protocol Version 3: 12-September-2016

PROTOCOL

TITLE:	**A PROSPECTIVE OPEN-LABEL STUDY OF THE EFFECTIVENESS OF EPOETIN BETA FOR TREATING ANEMIC PATIENTS WITH LOW/INTERMEDIATE-1-RISK MYELODYSPLASTIC SYNDROME (MDS)**
PROTOCOL NUMBER:	ML29005
VERSION NUMBER:	3.0
EUDRACT NUMBER:	N/A
IND NUMBER:	N/A
TEST PRODUCT:	Epoetin beta (RO205-3859)
MEDICAL MONITOR:	Dr. [redacted], MD.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 3.0: 26 July 2016
DATE AMENDED:	Version 1.0: 16 Dec 2013 Version 2.0: 28 Jul 2014 Version 3.0: See electronic date stamp below

PROTOCOL AMENDMENT APPROVAL

Name	Signature	Date
[redacted] MD	[redacted]	12 Sept. 2016

PROTOCOL AMENDMENT, VERSION 3.0: RATIONALE

Protocol ML29005 has been amended to extend study duration and to improve clarity and consistency on dose adjustment.

Changes to the protocol, along with a rationale for each change, are summarized below:

- Protocol synopsis, section the length of study is updated to extend recruitment duration to reach original target patients, 120 patients.
- Section 4.2.2.1 is updated to clarify criteria for dose adjustment due to changes in the level of haemoglobin at week 4 (visit 2)
- Section 4.2.4 Post-study access to Recormon® is updated according to Roche global post-study access policy
- Section 5.4, 5.4.1 and 5.4.2 is updated due to changes in Medical Monitor (Roche Medical Responsible) and local safety responsible person's contact detail
- Section 6.2, 6.4 and 6.4.1 is updated in the efficacy analysis population. As there is apparently no randomization in the study, the Intent-To-Treat population can be applied.

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

PROTOCOL AMENDMENT, VERSION 3.0: SUMMARY OF CHANGES

PROTOCOL TITLE PAGE

VERSION: ~~2~~3

FOOTER:

Recormon—F. Hoffmann-La Roche Ltd
Protocol ML29005, ~~Version 2.0 dated 28 Nov 2014~~ Version 3.0 dated 26 July 2016

PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes to the protocol, where applicable.

SECTION 3.1.1: Overview of Study Design

This is a phase IV, prospective, multi-centre, open label study to assess the efficacy of Recormon® for treating anemic patients with low/intermediate-1 risk MDS, in approximately 120 adult patients. The primary efficacy endpoint is a proportion of patients achieving erythroid response at week 12 according to IWG 2006 definition. The trial will be conducted at approximately ~~7~~8 centres nationwide.

SECTION 3.3.2: Rational for Patient Population

Several studies have proven the efficacy of the ESAs in eliciting erythroid response in low/int-1 MDS patients. The subset of MDS patients benefiting from ESA therapy is now well defined as the low-/int-1-risk group with sEPO of less than 500 mU/ml and a PRBC transfusion need of less than ~~two units/month~~ 4 units within 8 weeks prior to screening.

SECTION 4.2.2.1: Dosage and administration of Recormon®

Response will be firstly evaluated at ~~4±1 weeks~~ week 4 (visit 2)

- If haemoglobin level reaches ≥ 12 g/dL at any time, Recormon® should be discontinued until Hb levels are ≤ 10 g/dL
- If the haemoglobin level increases < 1 g/dL from ~~baseline~~ screening level and haemoglobin level < 12 g/dL, a 60,000 IU weekly of Recormon® will be administered subcutaneously until week 12.
- If the haemoglobin level increases ≥ 1 g/dL from ~~baseline~~ screening level and haemoglobin level < 12 g/dL, a 30,000 IU weekly of Recormon® will be continued until week 12

SECTION 4.2.4: Post-study Access to Recormon®

~~The Sponsor may provide Recormon® upon physician request to patients who have shown a demonstrable benefit from Recormon® treatment during this study (as showed by IWG 2006 response criteria; Hb increase ≥ 1.5 g/dL from baseline and Hb level at~~

~~week 12 range from 10 - 12 g/dL).~~The Sponsor will offer post-study access to the study drug (Recormon®) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive study drug after completing the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued study drug treatment for his or her well-being
- There are no appropriate alternative treatments available to the patient
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them

A patient will not be eligible to receive study drug after completing the study if any of the following conditions are met:

- The study drug is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient)
- The Sponsor has discontinued development of the study drug or data suggest that the study drug is not effective for low/intermediate-1 risk MDS
- The Sponsor has reasonable safety concerns regarding the study drug as treatment for low/intermediate-1 risk MDS
- Provision of study drug is not permitted under the laws and regulations of the patient's country

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following Web site:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

SECTION 5.4: IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Emergency Medical Contact:

Medical Monitor (Roche Medical Responsible) contact Information

Medical Monitor: Dr [redacted] MD.

Telephone [redacted]

SECTION 5.4.1: Reporting Requirements for Serious Adverse Events

Local safety responsible

Fax: [redacted]

Email: thailand.drug_safety@roche.com

SECTION 5.4.2: Reporting Requirements for Pregnancies

Local safety responsible

Fax: [redacted]

Email: thailand.drug_safety@roche.com

SECTION 6.2: ANALYSIS POPULATION

~~The Per Protocol (PP) population will include patients who complete 12 week treatment with no experience of any major protocol violations. Efficacy endpoints will be summarized based on PP population.~~ The efficacy analysis will be performed based on the intent-to-treat (ITT) population defined as all enrolled patients who receive at least one dose of study medication.

The Safety population will include all patients who receive at least one dose of study medication.

SECTION 6.4: EFFICACY ANALYSIS

The efficacy analyses will include all enrolled patients who receive at least one dose of study medication. Efficacy endpoint will be summarized based on ITT population. ~~The efficacy analyses will include all enrolled patients who complete end of study visit with no experience of any major protocol violations. Efficacy endpoints will be summarized based on PP population.~~ Subgroup analysis may be performed for efficacy analysis.

SECTION 6.4.1: Primary Efficacy Endpoint

The ~~Per Protocol (PP)~~ intent-to-treat (ITT) analysis of the primary outcome variables is planned. Patients who meet the evaluable criteria as specified in the analysis plan will be included in the per protocol

SAMPLE INFORMED CONSENT FORM

The sample Informed Consent Form has been revised to reflect the changes to the protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

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PROTOCOL NUMBER:	ML29005
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EUDRACT NUMBER:	RO205-3859
IND NUMBER:	N/A
TEST PRODUCT:	Epoetin beta (RO205-3859)
MEDICAL MONITOR:	Dr. [redacted], MD.
SPONSOR:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy as instructed by your local study monitor

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PROTOCOL SYNOPSIS

TITLE:	**A PROSPECTIVE OPEN-LABEL STUDY OF THE EFFECTIVENESS OF EPOETIN BETA FOR TREATING ANEMIC PATIENTS WITH LOW/INTERMEDIATE-1-RISK MYELODYSPLASTIC SYNDROME (MDS)**
PROTOCOL NUMBER:	ML29005
VERSION NUMBER:	3.0
EUDRACT NUMBER:	RO205-3859
IND NUMBER:	N/A
TEST PRODUCT:	Epoetin beta
PHASE:	IV
INDICATION:	Symptomatic anemia associated with Myelodysplastic Syndromes (MDS)
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives

Efficacy Objectives

To assess the efficacy of Recormon® for treating anemic patients with low/intermediate-1 risk MDS, as measured by erythroid response

Safety Objectives

To assess the safety profile of Recormon® for treating anemic patients with low/intermediate-1 risk MDS

Study Design

Description of Study

The study consists of a 2-week screening period, a 12-week treatment phase and end-of-study visit (see figure 1). After screening, eligible patients will be treated with epoetin beta (Recormon®) as recommended in the approved label and international guidelines for the use of epoetin in MDS patients, Recormon® dosage will be adjusted on the basis of erythroid response.

During screening period, serum level of endogenous erythropoietin will be assessed, as well as liver and kidney function. Bone marrow morphology analysis and karyotyping are also performed during screening if they have not been assessed in the 6 months prior to participation in the study. Complete blood count test is performed during screening period and at every patient's visit until the end of study visit. The result should be available on visit date, prior to the Recormon® administration

The patient's erythroid response will be assessed at week 4 and every 4 weeks thereafter, until end-of-study visit. Patients who achieve Hb level $\geq$ 12 g/dL will stop treatment, while patients with Hb level <12 g/dL will continue treatment for the total of 12 weeks. Concurrent G-CSF can be administered upon physician discretion.

Number of Patients

120 patients expected to be enrolled.

Target Population

Adult anemic MDS patients (⩾18 years old) in the low or intermediate-1 risk group according to the International Prognostic Scoring System (IPSS)

Inclusion Criteria

Patients must meet the following criteria for study entry:

1. Able and willing to provide written informed consent and to comply with the study protocol
2. Adult patients (≥ 18 years old)
3. Low or intermediate-1 risk MDS (having IPSS risk score ≤ 1) confirmed with bone marrow morphology analysis and karyotyping within 6 months prior to screening
4. No previous treatment with hematopoietic growth factors within 3 months prior to screening
5. Symptomatic anemia (Hb < 10 g/dL) as determined by investigator
6. Serum Erythropoietin < 500 mU/ml within 14 days prior to the first dose of study treatment.
7. Require no red blood cell transfusion or dependent on <4 units within 8 weeks prior to screening
8. Clinically stable for at least one month prior to entry into the study as determined by investigator
9. For female patients of childbearing potential and male patients with partners of childbearing potential, agree (by patient and/or partner) to use highly effective form(s) of contraception (i.e., one that results in a low failure rate [< 1% per year] when used consistently and correctly)

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

10. Contraindications and/or known hypersensitivity to the active substance and/or any of the excipients of Recormon® treatment according to the approved package insert.
11. Poorly controlled hypertension as assessed by the investigator
12. History of Acute myeloid leukemia (AML) or high risk for AML
13. Previously documented evidence of Pure red cell aplasia (PRCA)
14. Current pregnancy or breast-feeding
15. High likelihood of early withdrawal or interruption of the study
16. Administration of another investigational drug within 1 month before screening or planned during the study period

Length of Study

It is expected that approximately 120 patients will be enrolled, over approximately 48 months.

The study is estimated to last approximately 4.5 years, based on an expected 48-month recruitment period, up to 3 months of study treatment and a month of follow-up after the completion of the last study treatment

End of Study

The end of the study is defined as the date when the last patient, last visit (LPLV) occurs, that is when the last patient reaches the end-of-study visit (approximately 4 months after the last patient is enrolled). The end-of-study visit will occur 4 weeks after patient's last dose of study treatment, or earlier if one of the following is documented for all treated patients: withdrawal from the study, loss to follow up or death

Efficacy Outcome Measures

The efficacy outcome measures for this study are:

Primary Efficacy Outcomes:

- The cumulative proportion of patients achieving erythroid response at week 12 according to IWG 2006 definition as
- Hb increase by $\geqslant$ 1.5 g/dL
- Reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 weeks compared with the pre-treatment transfusion number in the previous 8 weeks. Only RBC transfusions given for a Hb of $\leqslant$ 9.0 g/dL pre-treatment will count in the RBC transfusion response evaluation

Secondary Efficacy Outcomes:

- % patients with platelet response (pre-treatment < 100×109/L) at week 12 defined by IWG 2006 as following;
- Absolute increase of ≥ 30 x 109/L for patients starting with > 20 x 109/L platelets (Increase from < 20 x 109/L to > 20 x 109/L and by at least 100%)
- % patients with neutrophil response (pre-treatment < 1.0 x 109/L) at week 12 defined by IWG 2006 as following;
- At least 100% increase and an absolute increase > 0.5 x 10^9/L

Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Tolerability and safety of Recormon®

Investigational Medicinal Products

Injectable solution of Recormon® (provided free of charge by Roche) 30,000 or 60,000 IU per week administered subcutaneously

The initial dose is 30,000 IU per week administered subcutaneously

- Response will be firstly evaluated at week 4 (visit 2):
  - If haemoglobin level $\geq$ 12 g/dL at any time, Recormon® should be discontinued until Hb levels are ≤ 10 g/dL
  - If the haemoglobin level increases < 1 g/dL from screening level and haemoglobin level < 12 g/dL, a 60,000 IU weekly of Recormon® will be administered subcutaneously until week 12
  - If the haemoglobin level increases $\geq$ 1 g/dL from screening level and haemoglobin level < 12 g/dL, a 30,000 IU weekly of Recormon® will be continued until week 12

Non-Investigational Medicinal Products

Upon physician discretion, G-CSF can be used concurrently

Statistical Methods

Descriptive statistics will be used for baseline characteristics. The interim data analysis will be performed when the first 30 patients completing 12-week treatment period.

Determination of sample size

Sample size based on a 5% significance level and the 80% power with 10% drop out resulting of 120 patients in total.

Safety: Assuming a 10% withdrawal rate, 120 patients will be enrolled such that we expect 108 patients will not withdraw and will remain evaluable. With 108 evaluable patients in this study, the sample size is sufficient to have at least 95% probability of observing a particular adverse event in at least one patient in this study, if the true proportion of patients in the target population as a whole who experience this event is 0.0274 i.e. approximately 1 in every 37 patients.

Efficacy: Assuming a 10% withdrawal rate, 120 patients will be enrolled such that we expect 108 patients will not withdraw and will remain evaluable. To give an estimate of the precision of this study in terms of estimating the proportion of patients with erythroid response, then with 108 evaluable patients in this study, if the observed proportion of patients with erythroid response in the study were 0.25, then the half width of the 95% confidence interval for this proportion would be 0.0817 (i.e. the 95% confidence interval would be 0.1683 to 0.3317).

Analysis Population

The efficacy analysis will be performed based on the intent-to-treat (ITT) population defined as all enrolled patients who receive at least one dose of study medication.

The Safety population will include all patients who receive at least one dose of study medication.

Interim Analysis

An interim analysis of primary end point (erythroid response at week 12 according to IWG 2006 definition) will be undertaken when the first 30 patients have completed their 12-week treatment, and safety data will also be summarized at that time.

Further details regarding the planned interim analysis will be presented in the Statistical Analysis Plan (SAP).

Efficacy Analysis

The efficacy analyses will include all enrolled patients who receive at least one dose of study medication. Efficacy endpoint will be summarized based on ITT population. Subgroup analysis may be performed for efficacy analysis.

Primary Efficacy Endpoint

Intent-To-Treat (ITT) analysis of the primary outcome variables is planned. Patients who meet the evaluable criteria as specified in the analysis plan will be included in the per protocol

For the primary endpoint of erythroid response, the percentages of patients who achieve the target haemoglobin increase by $\geq$ 1.5 g/dL, or reduction of units of RBC transfusions by an absolute number at week 12 will be summarized in table.

Secondary Efficacy Endpoints

Secondary efficacy endpoints include platelet and neutrophil response at week 12, defined by the following IWG 2006 criteria and will analyzed for the PP population.

- % patients with platelet response (pre-treatment < 100×10^9/L) at week 12 defined by IWG 2006 as following;
- Absolute increase of ≥ 30 x 109/L for patients starting with > 20 x 109/L platelets (Increase from < 20 x 109/L to > 20 x 109/L and by at least 100%)
- % patients with neutrophil response (pre-treatment < 1.0 x 109/L) at week 12 defined by IWG 2006 as following;

- At least 100% increase and an absolute increase > 0.5 x 109/L

The percentages of patient who achieve the above hematologic responses at week 12, according to the IWG 2006 criteria will be presented in summary tables.

Safety Analyses

All patients who have received at least one dose of study medication, whether prematurely withdrawal or not will be included in the safety analysis.

The safety parameters will be vital signs, AEs, SAEs and the safety laboratory assessments including serum ferritin. All clinical AEs and SAEs as well as laboratory abnormalities will be recorded and graded according to the NCI-CTCAE version 4.0.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of all AEs/SAEs will be summarized according to the primary system-organ class and by preferred terms.

Safety laboratory parameters will be summarized and at least presented descriptively, and the selected laboratory parameters may also be displayed graphically.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse event
ALT/SGPT	Alanine Aminotransferase
AST/SGOT	Aspartate Aminotransferase
AML	Acute Myeloid Leukemia
ATRA	All-Trans Retinoic Acid
MDS	Myelodysplastic Syndromes
CBC	Complete Blood Count
CHO	Chinese Hamster Ovary
CKD	Chronic Kidney Disease
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
EC	Ethics Committee
ECG	Electrocardiography
eCRF	electronic Case Report Form
ESA	Erythropoiesis-stimulating agent
FDA	Food and Drug Administration
G-CSF	Granulocyte Colony-Stimulating Factor
GCP	Good Clinical Practice
Hb	Haemoglobin
EPO	Recombinant Erythropoietin
HSCT	Hematopoietic Stem Cell Transplantation
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
IND	Investigational New Drug
int-1	intermediate-1
int-2	intermediate-2
IPSS	International Prognostic Scoring System
IRB	Institutional Review Board
IWG 2006	International Working Group 2006
LPLV	last patient, last visit
NCI	National Cancer Institute
PRBCs	Packed Red Blood Cells
PRCA	Pure Red Cell Aplasia
QoL	Quality of Life
RBC	Red Blood Cells
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
sEPO	Serum Erythropoietin

Abbreviation	Definition
ULN	Upper Limit of Normal
WBC	White Blood Cell
WHO	World Health Organization
X-ray	X-radiation

1. BACKGROUND

1.1 BACKGROUND ON MYELODYSPLASTIC SYNDROMES

Myelodysplastic syndromes (MDS) are a group of hematological neoplastic diseases with a heterogeneous clinical presentation and, most probably, heterogeneous pathophysiology. Their common shared clinical feature is the presence of severe peripheral blood cytopenias, especially anaemia, and by frequent evolution to acute myeloid leukaemia (AML) (Fenaux 2004). In more than two thirds of MDS cases, anemia is present at diagnosis. Improving erythropoiesis, and thus eliminating fatigue and symptoms, is the main therapeutic target for the majority of MDS patients, because >50% of patients present with anemia with an Hb level <10 g/dL. Some 85% of patients develop more serious anemia as MDS progresses and >80% require red blood cell (RBC) transfusion. In a mainly geriatric population of patients, anemia leads to co-morbidities that include cardiac complications, increased fatigue, diminished quality of life (QoL), and the need for chronic RBC transfusion. Well-known problems associated with RBC transfusions are iron overload, fluctuating haemoglobin levels, and persistently low haemoglobin levels (usually <10 g/dL), in addition to the intrinsic risks related to intolerance reactions, alloimmunization, and infections.

Diagnostic and prognostic evaluations of MDS patients are based on the French–American–British classification (Bennett 1986), the derived International Prognostic Score System (IPSS) (Greenberg 1998), the World Health Organization (WHO) classification (Swerdlow et al. 2008), or the derived WHO classification-based prognostic scoring system, WPSS (Malcovati et al. 2007). These prognostic systems are strongly dependent on the morphological detection of immature cells and on the presence of cytogenetic abnormalities.

The International Prognostic Scoring System (IPSS) that accounts for cytogenetic, number of lineages involved in dysplasia and the bone marrow blast counts, divides MDS into four categories; low, intermediate-1 (int-1), intermediate-2 (int-2) and high risk for leukemic transformation and survival (Komrokji and Bennett 2007). The median survival is estimated at 5.7, 3.5, 1.2 and 0.4 years, respectively. The median time for leukemic transformation in at least 25% of patients is 9.4, 3.3, 1.1 and 0.2 years respectively.

Management of MDS is based on expectations of treatment tolerability and quality of life, as well as on the risks imposed by the disease itself. However, because MDS differs from many hematologic malignancies in terms of its chronic nature and in the morbidity and mortality associated with cytopenias, alleviating disease-related symptoms is an important therapeutic goal. Therapy can be optimized for each patient based on IPSS risk category as well as age, performance status, and comorbidities, all of which determine the likelihood of a patient tolerating treatments of different intensities. Relying on the major IPSS risk, groups of “lower-risk” disease encompasses low- and intermediate (Int)-1-risk categories, and “higher-risk” MDS incorporates those patients with Int-2-and High-risk disease.

A “watch and wait” approach is generally recommended for patients with lower-risk disease, a haemoglobin level >10 g/dL, and with no transfusion needs. Higher-risk patients usually require treatment immediately (Ria et al. 2009). Given that Hematopoietic stem cell transplantation (HSCT) is the only potentially curative treatment for MDS (Cheson et al. 2000), any initial decision must be made around the eligibility of the patient for transplantation. A key consideration in any patient with MDS is the need to avoid chronic transfusion dependency, because this is associated with iron overload and its attendant potential risk of organ damage and dysfunction (Ria et al. 2009 and Goldberg et al. 2010).

It is known that, at some point in the natural history of the disease, every MDS patient requires regular transfusions of packed red blood cells (PRBCs) and/or platelets to maintain peripheral blood cell counts. The proportion of PRBC transfusion-dependent patients increases with the severity of the disease from low- to high-risk MDS categories. Approximately 40–50% of patients are PRBC-transfusion-dependent in low-/int-1-risk groups, while the number rises to 65–80% in the int-2-/high-risk groups (Balducci 2006).

Transfusion dependency affects quality of life and predicts shortened survival (Goldberg et al. 2010 and Malcovati et al. 2007). Best supportive care for all patients includes clinical monitoring, red blood cell (RBC) and platelet transfusions for symptomatic anemia or thrombocytopenia, psychosocial support, and quality-of-life assessments. Daily iron chelation with subcutaneous deferoxamine or oral deferasirox should be considered to decrease iron overload in patients receiving >20 to 30 RBC transfusions. In addition, hematopoietic growth factor support, such as erythropoietin, granulocyte colony-stimulating factor, or granulocyte/macrophage colony-stimulating factor, should be considered for symptomatic cytopenias that are unresponsive to correction of all other identifiable causes of the low blood counts.

1.2 BACKGROUND ON EPOETIN BETA (RECORMON®)

Recormon® (epoetin beta) is a sterile, purified, stable recombinant human erythropoietin concentrate produced from genetically engineered chinese hamster ovary (CHO) cells containing a cloned human erythropoietin gene. Recormon® is provided as lyophilisate and solvent for solution for injection in cartridge, and as solution for injection in pre-filled syringes. The reconstituted product is a colorless, clear to slightly opalescent solution.

Epoetin beta is a glycoprotein that stimulates the proliferation and differentiation processes of the erythroid stem cell compartment and also has a stimulatory effect on the proliferation and maturation compartment of the erythron. Epoetin beta therefore leads to an increase in haemoglobin formation and an associated acceleration of cell maturation with reduction in the cell cycle time. A further effect of epoetin beta is the acceleration of reticulocyte maturation and an increase in the release of reticulocytes into the bloodstream.
Recormon® has been approved by Thai FDA for the following therapeutic Indication(s)

- Treatment of symptomatic anemia associated with chronic kidney disease (CKD) in patients on dialysis.
- Treatment of symptomatic renal anemia in patients not yet undergoing dialysis.
- Prevention of anemia of prematurity in infants with a birth weight of 750 to 1500 g and a gestational age of less than 34 weeks.
- Treatment of symptomatic anemia in adult patients with non-myeloid malignancies receiving chemotherapy.
- Increasing the yield of autologous blood from patients in a pre-donation program.
- Its use in this indication must be balanced against the reported increased risk of thromboembolic events. Treatment should only be given to patients with moderate anemia (Hb 10 - 13 g/dL [6.21 - 8.07 mmol/l], no iron deficiency) if blood conserving procedures are not available or insufficient when the scheduled major elective surgery requires a large volume of blood (4 or more units of blood for females or 5 or more units for males).
- Treatment of symptomatic anemia associated with Myelodysplastic Syndromes (MDS) patients, including other ineffective erythropoiesis

See the local prescribing information for more details.

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

Chronic refractory anemia and long-term use of blood transfusions pose a tremendous clinical and economic burden to the management of MDS patients. Thus, treatment options aimed at maintaining transfusion independence or delaying transfusion dependence play an important role in the management of low-risk early disease.

Of the currently available therapeutic options, Erythropoiesis-stimulating agents (ESAs) alone or in combination with GCSF appear to fulfill this goal in a significant proportion of MDS patients. In contrast to the application of these growth factors to treat the side effects of chemotherapy in other cancers, their use in MDS appears to serve a therapeutic role since ineffective hematopoiesis, and specifically defective erythropoiesis, constitute the basic pathology in MDS. By promoting survival and differentiation ESAs overcome excessive apoptosis of erythroid progenitors and, hence, are therapeutic in alleviating the basic pathology of these disorders.

Recombinant erythropoietin (EPO) can correct anaemia in about 20% of MDS when used alone and 40% when combined with recombinant human granulocyte colony-stimulating factor (G-CSF), and the response rate to EPO + G-CSF is higher than that of symptomatic treatment (Economopoulos et al. 1999, Remacha et al. 1999, Hellstrom-Lindberg et al. 2003, and Casadevall et al. 2004). Major prognostic factors for a favourable response to EPO ± G-CSF are low endogenous serum EPO levels (<200 or 500 U/l) and relatively low transfusion requirement. In patients with a serum EPO level below 500 U/l, response rates to EPO + G-CSF reach 60% (Hellstrom-Lindberg et al. 2003 and Casadevall et al. 2004).

Result from prospective randomized phase III trial by the Eastern Cooperative Oncology Group (E1996) confirm earlier studies by demonstrating the efficacy of adding G-CSF to EPO and higher EPO dose for enhancing erythroid responses in MDS (Greenberg et al. 2009). Mo yo et al. (Mo yo et al. 2007) also suggest increasing EPO dose may have a greater impact on erythroid responses than addition of G/GM-CSF.

Three ESAs have been used in MDS, epoetin-α and darbepoetin-α in the USA, and in addition epoetin-β outside of the USA. Several studies have proven the efficacy of these ESAs in eliciting erythroid response in low/int-1 MDS patients (MundLe 2006). A pretherapy endogenous serum erythropoietin (sEPO) level of less than 500 mU/ml and transfusion requirement of less than two units/month appear to predict the best response to ESA therapy, particularly in low/int-1 disease. As reviewed previously, with the use of these criteria for patient selection and that of the standardized response evaluation criteria recommended by the International Working Group in MDS, erythroid response rates have significantly improved to nearly 60–65% from approximately 20% in the past with their earlier use in unselected all-comer MDS patients evaluated for response with variable criteria (MundLe 2006). The responses to ESA alone, or in combination with granulocyte colony-stimulating factor (GCSF), appear to be remarkably durable with a median of 23 months in the absence of transfusions (Jadersten et al. 2005). The responses are observed both in transfusion-dependent patients in terms of transfusion avoidance and Hb improvement, as well as in transfusion-independent patients in terms of Hb improvement.

It is evident that complete transfusion independence is achieved in 30–50% of patients, with a noticeable decrease in the mean number of PRBC units required to maintain Hb in others.

To date, no treatment-related side effects have been noted with ESA therapy and treatment with ESAs appears to be well-tolerated. In fact, the only largest randomized placebo-

controlled trial with ESA in MDS conducted thus far showed that the patients treated with EPO as a single agent had numerically lower rates of adverse events (32%) compared with those on placebo (43%) (ITALIAN COOPERATIVE STUDY GROUP 1998). Furthermore, encouragingly, no treatment-related episodes of thrombosis or seizures were reported in this trial or even after long-term administration of EPO to MDS patients in another large, single-arm trial (Terpos et al. 2002). The noticeable absence of therapy-related thrombotic events with EPO treatment of MDS in several clinical trials so far is indeed distinguished from even the minimum acceptable risk of thrombotic complications of ESAs when used in chemotherapy-induced anemia as listed in the drug prescribing information for epoetin-α or darbepoetin-α. Thus, treatment of MDS with ESA in general seems to be well tolerated with significant clinical benefits in MDS.

ESA use in MDS is widespread; recent estimates suggest that 60% of MDS patients received ESAs (Sekeres et al. 2008). The last update of the 2011 National Comprehensive Cancer Network guidelines (Greenberg et al. 2011) acknowledges the fact that anemia is a major issue in MDS patients to be addressed even more carefully than in the past with parallel statements by the Italian Society of Hematology (Alessandrino et al 2002), the United Kingdom (UK) MDS Guidelines Group (Bowen et al. 2003), Nordic MDS Group (Guideline by NMDS group), and the Thai MDS study group (Guideline by The Thai Society of Hematology).

As improvements in haemoglobin are usually noted 6–8 weeks after initiation of an adequate dose of ESA, a minimum 8-week therapeutic trial was considered to be indicated. Moreover, it should be noted that ESA doses found to impact the anemia of MDS are substantially higher than those used in chronic renal insufficiency (Oliva et al. 2010). The addition of granulocyte colony-stimulating factor (G-CSF), thought to synergize with ESA in producing an erythropoietic effect in MDS patients, is suggested for patients who do not manifest a response to ESA (Jadersten et al. 2008 and Hellstrom-Lindberg et al. 2003).

The relative durable clinical benefits and lack of adverse effects on survival or rate of leukemic transformation may uniquely position ESAs as the eminent therapeutic choice. Importantly, the subset of MDS patients benefiting from ESA therapy is now well defined as the low-/int-1-risk group with sEPO of less than 500 mU/ml and a PRBC transfusion need of less than two units/month. From a benefit–risk perspective, the positive long-term outcomes demonstrated with ESAs in a specified group of MDS patients have yet to be shown with other therapies. ESAs thus remain a treatment of choice for low-/int-1 MDS patients when considered against the significant risks and estimated high costs associated with complicated chronic blood transfusions.

However, the majority of clinical studies of ESAs in MDS patients use EPO-alpha. Few data have been published for EPO-beta. This prospective study aim to provide the additional effectiveness and safety profile of Recormon® (EPO-beta) for treatment of symptomatic anemia associated with MDS patients for all epoetin formulations review by Thai FDA.

2. OBJECTIVES

2.1 EFFICACY OBJECTIVES

The primary efficacy objective for this study is:

- To assess the efficacy of Recormon® for treating anemic patients with low/intermediate-1 risk MDS, as measured by erythroid response

2.2 SAFETY OBJECTIVES

The safety objective for this study is:

- To assess the safety of Recormon® for treating anemic patients with low/intermediate-1 risk MDS

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

3.1.1 Overview of Study Design

This is a phase IV, prospective, multi-centre, open label study to assess the efficacy of Recormon® for treating anemic patients with low/intermediate-1 risk MDS, in approximately 120 adult patients. The primary efficacy endpoint is a proportion of patients achieving erythroid response at week 12 according to IWG 2006 definition. The trial will be conducted at approximately 8 centres nationwide.

All potential study patients must provide signed written informed consent approved by the relevant independent Ethics Committee before undergoing any study-specific procedures. Results of the screening assessments must be available and patients must meet all eligibility criteria prior to enrolment into the study. The study design is shown in Figure 1.

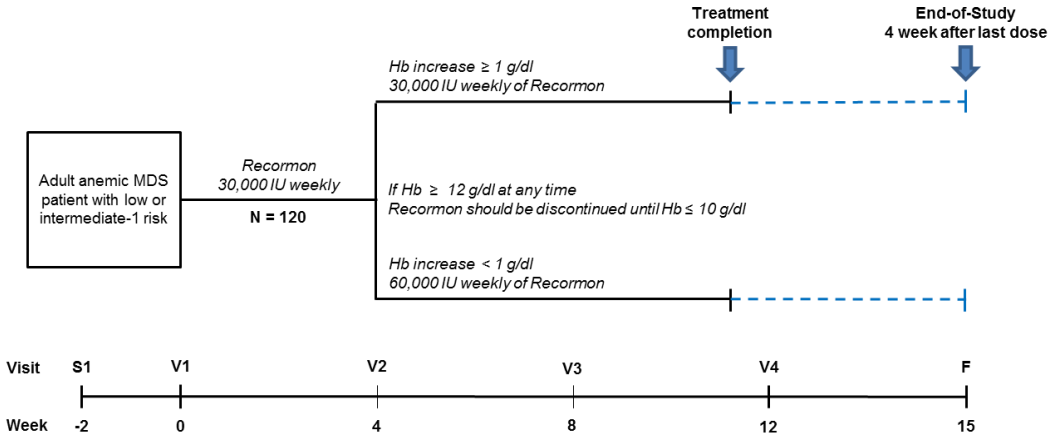

Figure 1 Study Scheme

The study consists of a 2-week screening period, a 12-week treatment phase and end-of-study visit (see figure 1). After screening, eligible patients will be treated with epoetin beta (Recormon®) as recommended in the approved label and international guidelines for the use of epoetin in MDS patients, Recormon® dosage will be adjusted on the basis of erythroid response.

During screening period, serum level of endogenous erythropoietin will be assessed, as well as liver and kidney function. Bone marrow morphology analysis and karyotyping are also performed during screening if they have not been assessed in the 6 months prior to participation in the study. Complete blood count test is performed during screening period and at every patient's visit until the end of study visit. The result should be available prior to dosing of Recormon®.

The patient's erythroid response will be assessed at week 4 and every 4 weeks thereafter, until end-of-study visit. Patients who achieve Hb level ≥ 12 g/dL will stop treatment, while

patients with Hb level < 12 g/dL will continue treatment for the total of 12 weeks. Concurrent G-CSF can be administered upon physician discretion.

Patients can withdraw from the study at any time as per section 4.5.1

Study oversight will be assured by a steering committee to guide study conduct, to review the results at the end of the study, to approve and sign-off the study report and to prepare and submit a publication to a peer-review journal. The steering committee will be made up of investigators and Roche representatives and will meet at regular intervals.

A schedule of assessments is provided in Appendix 1.

3.2 END OF STUDY

The end of the study is defined as the date when the last patient, last visit (LPLV) occurs, that is when the last patient reaches the end-of-study visit (approximately 4 months after the last patient is enrolled). The end-of-study visit will occur 4 weeks after patient's last dose of study treatment, or earlier, if one of the following is documented for all treated patients: withdrawal from the study, loss to follow up or death.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Test Product Dosage

The study treatment dosing is consistent with the approved label of Recormon® and standard treatment guidelines.

As improvements in haemoglobin are usually noted 6–8 weeks after initiation of an adequate dose of ESA, a minimum 8-week treatment period was considered to be indicated.

3.3.2 Rationale for Patient Population

Several studies have proven the efficacy of the ESAs in eliciting erythroid response in low/int-1 MDS patients. The subset of MDS patients benefiting from ESA therapy is now well defined as the low-/int-1-risk group with sEPO of less than 500 mU/ml and a PRBC transfusion need of less than 4 units within 8 weeks prior to screening.

3.4 OUTCOME MEASURES

3.4.1 Efficacy Outcome Measures

The efficacy outcome measures for this study are as follows:

Primary Efficacy Outcomes:

- The cumulative proportion of patients achieving erythroid response at week 12 according to IWG 2006 definition as
  - Hb increase by $\geqslant$ 1.5 g/dL
  - Reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 weeks compared with the pre-treatment transfusion number in the previous 8 weeks. Only RBC transfusions given for a Hb of $\leqslant$ 9.0 g/dL pre-treatment will count in the RBC transfusion response evaluation

Secondary Efficacy Outcomes:

- % patients with platelet response (pre-treatment < 100×109/L) at week 12 defined by IWG 2006 as following;
  - Absolute increase of ≥ 30 x 10^9/L for patients starting with > 20 x 10^9/L platelets (Increase from < 20 x 10^9/L to > 20 x 10^9/L and by at least 100%)
- % patients with neutrophil response (pre-treatment < 1.0 x 10^9/L) at week 12 defined by IWG 2006 as following;
  - At least 100% increase and an absolute increase > 0.5 x 10^9/L

3.4.2 Safety Outcome Measures

The safety outcome measures for this study are as follows:

Tolerability and safety of Recormon® (Incidence, nature, and severity of adverse events)

Safety assessments will include AEs, SAEs, routine safety laboratory tests, vital signs measurements, and recording of concomitant medications. All clinical AEs and SAEs as well as laboratory abnormalities will be recorded and graded according to the NCI-CTCAE version 4.0.

Patients will undergo an end-of-study safety assessment 4 weeks after the last Recormon® administration or after early withdrawal (unless the reason for early withdrawal is withdrawal of consent)

4. MATERIALS AND METHODS

4.1 PATIENTS

Adult anemic MDS patients (⩾18 years old) in the low or intermediate 1 risk group according to the International Prognostic Scoring System (IPSS)

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Able and willing to provide written informed consent and to comply with the study protocol
- Adult patients (≥ 18 years old)
- Low or intermediate-1 risk MDS (having IPSS risk score ≤ 1) confirmed with bone marrow morphology analysis and karyotyping within 6 months prior to screening
- No previous treatment with hematopoietic growth factors within 3 months prior to screening
- Symptomatic anemia (Hb < 10 g/dL) as determined by investigator
- Serum Erythropoietin < 500 mU/ml within 14 days prior to the first dose of study treatment
- Require no red blood cell transfusion or dependent on < 4 units within 8 weeks prior to screening
- Clinically stable for at least one month prior to entry into the study as determined by investigator
- For female patients of childbearing potential and male patients with partners of childbearing potential, agree (by patient and/or partner) to use highly effective form(s)

of contraception (i.e., one that results in a low failure rate [< 1% per year] when used consistently and correctly)

4.1.2 Exclusion Criteria

- Patients who meet any of the following criteria will be excluded from study entry:
- Contraindications and/or known hypersensitivity to the active substance and/or any of the excipients of Recormon® treatment according to the approved package insert
- Poorly controlled hypertension as assessed by the investigator
- History of Acute myeloid leukemia (AML) or high risk for AML
- Previously documented evidence of Pure red cell aplasia (PRCA)
- Current pregnancy or breast-feeding
- High likelihood of early withdrawal or interruption of the study
- Administration of another investigational drug within 1 month before screening or planned during the study period

4.2 STUDY TREATMENT

4.2.1 Formulation, Packaging, and Handling

4.2.1.1 Recormon®

Recormon® will be supplied by the sponsor as solution for injection in pre-filled syringes.

For further details, see the local prescribing information.

4.2.2 Dosage, Administration and Compliance

4.2.2.1 Dosage and administration of Recormon®

Injectable solution of Recormon® 30,000 or 60,000 IU per week administered subcutaneously

The initial dose is 30,000 IU per week administered subcutaneously

Response will be firstly evaluated at week 4 (visit 2):

- If haemoglobin level reaches ≥ 12 g/dL at any time, Recormon® should be discontinued until Hb levels are ≤ 10 g/dL
- If the haemoglobin level increases < 1 g/dL from screening level and haemoglobin level < 12 g/dL, a 60,000 IU weekly of Recormon® will be administered subcutaneously until week 12.
- If the haemoglobin level increases ≥ 1 g/dL from screening level and haemoglobin level < 12 g/dL, a 30,000 IU weekly of Recormon® will be continued until week 12

4.2.2.2 Assessment of Compliance

Accountability and subject compliance will be assessed by maintaining adequate drug dispensing and return records. Subjects will be instructed on how to self-inject at the screening visit and re-instructed at each visit if deemed necessary by the Investigator/delegate.

A Drug Inventory/Dispensing Log provided by Roche must be kept current and should contain the following information at a minimum:

- the identification of the subject to whom the study medication was dispensed
- the date[s], quantity of the study medication dispensed to the subject
- the initials of the person confirming administration of the study medication
- the date[s] and quantity of the study medication returned by the subject

This inventory must be available for ongoing inspection by the Monitor. In case of home administrations, for assessment of compliance, subjects will be asked to return all used and unused drug supply boxes to the investigational site at each visit. The compliance will be assessed by reconciliation of the number of unused syringes and empty drug supply boxes returned. Immediately after self-injection by the subject, the used syringes must be placed in a safety container provided by Roche. This safety container should be returned to the investigational site at each visit for immediate disposal by site staff in accordance with the study site's institutional standard operating procedure

4.2.3 Investigational Medicinal Product Accountability

Recormon® will be provided by the Sponsor. The investigational site will acknowledge receipt of IMPs to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedures or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed upon by the Sponsor. The site must obtain the written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.2.4 Post-study Access to Recormon®

The Sponsor will offer post-study access to the study drug (Recormon®) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive study drug after completing the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued study drug treatment for his or her well-being
- There are no appropriate alternative treatments available to the patient
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them

A patient will not be eligible to receive study drug after completing the study if any of the following conditions are met:

- The study drug is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient)
- The Sponsor has discontinued development of the study drug or data suggest that the study drug is not effective for low/intermediate-1 risk MDS
- The Sponsor has reasonable safety concerns regarding the study drug as treatment for low/intermediate-1 risk MDS
- Provision of study drug is not permitted under the laws and regulations of the patient's country

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following Web site:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.3 CONCOMITANT THERAPY

4.3.1 Permitted Therapy

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, nutritional supplements) used by a patient from 4 weeks prior to screening to the end-of-study visit/early termination visit.

Throughout the study, patient could be treated with any concomitant medications or treatment necessary to provide adequate supportive care except for those treatments listed in the prohibited therapy. Upon physician discretion and their normal practice, G-CSF can be used.

All RBC transfusions administered during the study should be documented (i.e., specified by number of units transfused) and recorded on the eCRF.

All concomitant medications should be reported to the investigator and recorded on the Concomitant Medications electronic Case Report Form (eCRF).

4.3.2 Prohibited Therapy

The following treatments are prohibited during study treatment:

Investigational or unlicensed/unapproved agents of any type

Patients receiving any of the prohibited therapies will be discontinued and assessed for safety at end-of study visit

4.4 STUDY ASSESSMENTS

4.4.1 Description of Study Assessments

For the timing of each assessment listed in this section, refer to Section 4.4.2 and Appendix 1.

4.4.1.1 Medical History and Demographic Data

Medical history includes clinically significant diseases and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements)

used by the patient within 4 weeks prior to the screening visit. RBC transfusion needed within 8 weeks prior to the screening will be recorded.

Demographic data will include weight, height, age and gender.

4.4.1.2 Physical Examinations

A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Any abnormalities identified at screening should be recorded on the General Medical History and Baseline Conditions eCRF.

At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.4.1.3 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, and body temperature.

4.4.1.4 Laboratory Assessments

Samples for the following standard laboratory tests will be sent to the study site's local laboratory for analysis. The results from these assessments should be available on visit date, prior to the Recormon® administration:

- Haematology parameters will include haemoglobin (Hb), red blood cell count (RBC), white blood cell count (WBC) and differentials, and platelet count.
- Biochemistry parameters at screening will include serum EPO, serum creatinine, alanine aminotransferase (ALT/SGPT) and aspartate aminotransferase (AST/SGOT). Biochemistry parameters at any further time point during the study will include ALT/SGPT, AST/SGOT, and serum creatinine. Serum ferritin will include at screening and end-of-study visit.

4.4.2 Timing of Study Assessments

4.4.2.1 Screening Assessments

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

Screening tests and evaluations will be performed within 14 days prior to the start of study drug administration, unless otherwise specified.

Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 14 days prior to the start of study drug administration may be used; such tests do not need to be repeated for screening. These will include the following:

- Review and documentation of demographics data and medical history
- Review and documentation of MDS diagnosis
- IPSS score
- Physical examination
- Vital sign measurements
- Haematology and biochemistry laboratory tests
- AE recording (Note: after informed consent has been obtained but prior to initiation of study drug, only SAEs caused by a protocol-mandated intervention should be reported).
- Recording concomitant treatments and therapies
- Recording RBC transfusion needed within the past 8 weeks
- Serum pregnancy test for female patients of childbearing potential. Patients who are amenorrheic for at least 12 months are not considered of childbearing potential.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrolment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Patients who fail screening may be re-screened if it is considered likely that they could later become eligible. There is a limit of 2 screening attempts for each patient. Re-consenting process must be performed.

Please see Appendix 1 for the schedule of screening assessments.

4.4.2.2 Assessments during Treatment

All assessments must be performed on the day of the specified visit (V1 – V4), unless a time window is specified in the schedule of assessments (see Appendix 1). Assessments scheduled on the visit date should be performed prior to administration of study treatment, unless otherwise noted in the schedule of assessments.

At each treatment visit, patients will undergo the following assessments:

- Physical examination and measurements of vital signs
- Routine laboratory tests (see section 4.4.1.4 for details about individual laboratory assays). The results from these tests should be available on visit date prior to the Recormon® administration.
- AE recording
- Recording concomitant treatments and therapies
- Recording RBC transfusion needed from previous visit
- Recormon® dose adjustment will be performed at week 4±1 (see section 4.2.2.1 for details about dose adjustment)

Please see Appendix 1 for the schedule of assessments performed during the treatment period.

4.4.2.3 Assessments at End of Study/Early withdrawal visit

End of study/early withdrawal visit will occur at 4 weeks after last dose of Recormon®. This visit will include the following evaluations:

- Physical examination and vital sign measurements
- Safety laboratory assessments (see section 4.4.1.4 for details about individual laboratory assays)
- AE recording
- Recording of concomitant treatments and therapies
- Recording of RBC transfusion needed from previous visit

Please see Appendix 1 for the schedule of assessments performed at the end-of-study visit/early termination visit.

4.4.2.4 Assessments at Unplanned Visits

Assessments other than those specified in Appendix 1, Schedule of Assessments, may be performed as clinically indicated. These assessments should be adequately documented.

4.5 PATIENT, STUDY AND SITE DISCONTINUATION

4.5.1 Patient Discontinuation

The investigator has the right to discontinue a patient from study drug or withdraw a patient from the study at any time. In addition, patients have the right to voluntarily discontinue study drug or withdraw from the study at any time for any reason. In case of such withdrawal, the reason(s) for withdrawal must be documented. Reasons for discontinuation of study drug or withdrawal from the study may include, but are not limited to, the following*:*

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study

4.5.1.1 Discontinuation from Study Drug

Reasons for study drug discontinuation may include, but are not limited to the following:

- Evolution into high-risk MDS or overt leukemia as determined by Investigator
- Withdrawal of consent by the patient
- Any significant AE that compromises the patient's ability to participate in the study
- Investigator or Sponsor determines it is in the best interest of the patient
- Intercurrent illness
- Treatment unresponsiveness
- Need for prohibited treatment
- Protocol violation
- Pregnancy

Patients who discontinue study drug prematurely will be asked to return to the clinic for the end-of-study visit (see Section 4.4.2.3).The primary reason for premature study drug

discontinuation should be documented on the appropriate eCRF. Patients who discontinue study drug prematurely will not be replaced.

4.5.1.2 Withdrawal from Study

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. Patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

4.5.2 Study and Site Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.
- Steering committee decision
- The Sponsor will notify the investigator if the study is placed on hold, or if the Sponsor decides to discontinue the study.
- The Sponsor has the right to replace a site at any time. Reasons for replacing a site may include, but are not limited to, the following:
- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Conference on Harmonization (ICH) guideline for Good Clinical Practice

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Patients will be assessed by prior medical history, vital signs (including resting blood pressure, heart rate, and body temperature), weight and height, physical examination, AEs and concomitant medications. A complete medical history (including prior treatments for MDS) will be documented at screening. A general physical exam will be performed at screening, and at every treatment visit and end-of-study visit (see Appendix 1, Schedule of Assessments).

AEs will be monitored and documented continuously during the study. SAEs will also be documented and reported according to the ICH E2 Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting. All AEs and SAEs (including patients' symptoms and signs of toxicity and clinically significant haematological and biochemical parameters) will be graded according to NCI CTCAE version 4.0.

Changes in concomitant medication will be recorded at each study visit.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events; measurement of protocol-specified safety laboratory assessments; and other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Fatal (i.e., the adverse event actually causes or leads to death)
- Life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)
- This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms “severe” and “serious” are not synonymous. Severity refers to the intensity of an adverse event (rated as mild, moderate, or severe, or according to NCI CTCAE criteria; see Section 5.3.2); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4 for reporting instructions) via appropriate SAE reporting form.

Related SAEs MUST be collected and reported regardless of the time elapsed from the last study treatment administration, even if the study has been closed.

Unrelated SAEs must be collected and reported during the study and for up to 28 days after the last dose of study medication.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.2), and causality (see Section 5.3.3).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient’s medical record and on the Adverse Event eCRF.

After informed consent has been obtained **but prior to initiation of study drug**, only serious adverse events caused by a protocol-mandated intervention should be reported

After initiation of study drug, all adverse events, regardless of relationship to study drug, will be reported until 4 weeks (28 days) after the last dose of study drug (End of study/early withdrawal visit)

Resolution of adverse events and serious adverse events including dates should be followed-up until it is known or end of study/early withdrawal visit, whichever occurs first and documented on the Adverse Events eCRF and in the patient’s medical record to facilitate source data verification.

5.3.2 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v4.0) will be used for assessing adverse event severity. Table 1 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 1 Adverse Event Severity Grading Scale

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
Note: Based on the NCI CTCAE (v4.0), which can be found at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding one's self, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4. for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4. for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.3 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly.

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.4 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.4.1 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.4.2 Adverse Events Occurring Secondary to Other Events

In general, adverse events occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. However, medically significant adverse events occurring secondary to an initiating event that are separated in time should be recorded as independent events on the Adverse Event eCRF.

5.3.4.3 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens. If the event becomes serious, the Adverse Event eCRF should be updated to reflect this.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded separately on the Adverse Event eCRF.

5.3.4.4 Abnormal Laboratory Values and Vital Sign Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

Accompanied by clinical symptoms

Results in a change in study treatment

Results in a medical intervention or a change in concomitant therapy

Clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings and vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality or an isolated vital sign abnormality should be classified as an adverse event.

5.3.4.5 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported.

If the death is attributed to progression of MDS, "MDS progression" should be recorded on the Adverse Event eCRF.

5.3.4.6 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors.

5.3.4.7 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

The following hospitalization scenarios are not considered to be serious adverse events:

- Hospitalization for respite care
- Planned hospitalization required by the protocol
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
  - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease
  - The patient has not suffered an adverse event

5.3.4.8 Overdoses

Study drug overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study drug is not an adverse event unless it results in untoward medical effects.

Any study drug overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF.

All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills serious criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4).

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

To ensure the safety of study patients, emergency Medical Call contact will be available 24 hours per day, 7 days per week. Medical Monitor contact information will be distributed to all investigators.

Emergency Medical Contact:

Medical Monitor (Roche Medical Responsible) contact Information

Medical Monitor: Dr. [redacted], MD.

Telephone: [redacted]

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events
- Pregnancies

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Reporting Requirements for Serious Adverse Events

For reports of serious adverse events, investigators should record all case details that can be gathered immediately (i.e., within 24 hours) on the Adverse Event page and

Forward the paper SAE reporting form via fax or email to:

Local safety responsible

Fax: [redacted]

Email: thailand.drug_safety@roche.com

5.4.2 Reporting Requirements for Pregnancies

No data are available from adequate, controlled studies of Recormon® in pregnant women. Therefore, women of childbearing potential must have a serum pregnancy test at screening and must use a reliable method of contraception throughout the study.

A female subject must be instructed to stop taking the study medication and immediately inform the investigator if she becomes pregnant during the study. The investigator should report all pregnancies within 24 hours after becoming aware of the pregnancy to the sponsor using the Pregnancy Reporting Form.

Forward the paper pregnancy reporting form via fax or email to:

Local safety responsible

Fax: [redacted]

Email: thailand.drug_safety@roche.com

The investigator should counsel the subject; discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Pregnancies occurring up to 90 days after the completion of the study medication must also be reported to the investigator.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

Descriptive statistics will be used for baseline characteristics. The interim data analysis will be performed when the first 30 patients are completing the 12-week treatment period.

6.1 DETERMINATION OF SAMPLE SIZE

Sample size based on a 5% significance level and the 80% power with 10% drop out resulting of 120 patients in total.

- Safety: Assuming a 10% withdrawal rate, 120 patients will be enrolled such that we expect 108 patients will not withdraw and will remain evaluable. With 108 evaluable patients in this study, the sample size is sufficient to have at least 95% probability of observing a particular adverse event in at least one patient in this study, if the true proportion of patients in the target population as a whole who experience this event is 0.0274 i.e. approximately 1 in every 37 patients.

- Efficacy: Assuming a 10% withdrawal rate, 120 patients will be enrolled such that we expect 108 patients will not withdraw and will remain evaluable. To give an estimate of the precision of this study in terms of estimating the proportion of patients with erythroid response, then with 108 evaluable patients in this study, if the observed proportion of patients with erythroid response in the study were 0.25, then the half width of the 95% confidence interval for this proportion would be 0.0817 (i.e. the 95% confidence interval would be 0.1683 to 0.3317).

6.2 ANALYSIS POPULATION

The efficacy analysis will be performed based on the intent-to-treat (ITT) population defined as all enrolled patients who receive at least one dose of study medication.

The Safety population will include all patients who receive at least one dose of study medication.

6.3 INTERIM ANALYSIS

An interim analysis of primary end point (erythroid response at week 12 according to IWG 2006 definition) will be undertaken when the first 30 patients have completed their 12-week treatment, and safety data will also be summarized at that time.

Further details regarding the planned interim analysis will be presented in the Statistical Analysis Plan (SAP).

6.4 EFFICACY ANALYSES

The efficacy analyses will include all enrolled patients who receive at least one dose of study medication. Efficacy endpoint will be summarized based on ITT population. Subgroup analysis may be performed for efficacy analysis.

6.4.1 Primary Efficacy Endpoint

The Intent-To-Treat (ITT) analysis of the primary outcome variables is planned. Patients who meet the evaluable criteria as specified in the analysis plan will be included in the per protocol

For the primary endpoint of erythroid response, the percentages of patients who achieve the target haemoglobin increase by ≥1.5 g/dL, or reduction of units of RBC transfusions by an absolute number at week 12 will be summarized in the table.

6.4.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints include platelet and neutrophil response at week 12, defined by the following IWG 2006 criteria and will analyzed for the PP population.

- % patients with platelet response (pre-treatment < 100×10^9/L) at week 12 defined by IWG 2006 as following;
    - Absolute increase of ≥ 30 x 10^9/L for patients starting with > 20 x 10^9/L platelets (Increase from < 20 x 10^9/L to > 20 x 10^9/L and by at least 100%)
- % patients with neutrophil response (pre-treatment < 1.0 x 10^9/L) at week 12 defined by IWG 2006 as following;
    - At least 100% increase and an absolute increase > 0.5 x 10^9/L

The percentages of patient who achieve the above hematologic responses at week 12, according to the IWG 2006 criteria will be presented in summary tables.

6.5 SAFETY ANALYSES

All patients who have received at least one dose of study medication, whether prematurely withdrawal or not will be included in the safety analysis.

The safety parameters will be vital signs, AEs, SAEs and the safety laboratory assessments including serum ferritin. All clinical AEs and SAEs as well as laboratory abnormalities will be recorded and graded according to the NCI-CTCAE version 4.0.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of all AEs/SAEs will be summarized according to the primary system-organ class and by preferred terms.

Safety laboratory parameters (Section 4.4.1.4) will be summarized and at least presented descriptively, and the selected laboratory parameters may also be displayed graphically.

Further details about planned safety analyses will be presented in Statistical Analysis Plan (SAP)

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will supply electronic eCRF specifications for this study. A contract research organization (CRO) will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC using eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will perform oversight of the data management of this study, including approval of the CRO's data management plans and specifications. Data will be periodically transferred electronically from the CRO to the Sponsor, and the Sponsor's standard procedures will be used to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored at the CRO and records retention for the study data will be consistent with the CRO's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed using a designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The investigational site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into an investigational site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.5).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, which includes an audit trail containing a complete record of all changes to data.

9.2 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRBs/ECs to inspect facilities and records relevant to this study.

9.3 ADMINISTRATIVE STRUCTURE

Please refer to the separate contact list for the contact information of the Sponsor CRO designee study personnel. This information can be found at the Roche Thailand Ltd. office, and within the Investigator Site File.

9.4 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor prior to submission. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.5 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1
Schedule of Assessments

	Screening	treatment phase				End-of-Study visit
Visit	**S1**	**V1**	**V2**	**V3**	**V4**	**F**
Week	**-2**	**0**	**4**	**8**	**12**	**15[a]**
Visit window ± (week)			**1**	**1**	**1**	**1**
Informed consent [b]	X					
Medical history	X					
Physical examination/vital signs	X	X	X	X	X	X
CBC[c]	X	X	X	X	X	X
Liver function test [d]	X	X	X	X	X	X
Creatinine	X	X	X	X	X	X
Serum EPO	X					
Serum Ferritin	X					X
Serum pregnancy [e]	X					
Record of RBC Transfusion	X	X	X	X	X	X
Concomitant treatment	X	X	X	X	X	X
Adverse event		X	X	X	X	X
Drug dispensing [f]		X	X	X		

[a] In case of early discontinuation, end-of-study for safety follow up must be undertaken 4 weeks after the last study drug administration (unless the reason for early withdrawal is withdrawal of consent)

[b] Written informed consent is required before performing any study-specific tests or procedures. Signing of the Informed Consent Form can occur outside the 14-day screening period.

[c] Parameters will include haemoglobin (Hb), red blood cell count (RBC), white blood cell count (WBC) and differentials, and platelet count

[d] Liver function test includes alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT)

All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening. Patients who are amenorrheic for at least 12 months are not considered of childbearing potential.

[f] If haemoglobin level reaches $\geq$ 12 g/dL at any time, Recormon® should be discontinued until Hb levels are $\leq$ 10 g/dL.

Appendix 2
International Prognostic Scoring System (IPSS)

(Greenberg et.al, 1997)

The 1997 International Prognostic Scoring System (IPSS) for De Novo Myelodysplastic Syndrome

Prognostic Factor	Category Score [a]				
	0 (best)	**0.5**	**1**	**1.5**	**2 (worst)**
Marrow Blasts	< 5%	5% - 10%	-	11% - 20%	21% - 30%
Karyotype	Good: Normal isolated –Y, isolated del(5q) or isolated del(20q)	Intermediate: All karyotypes not defined as Good or Poor	Poor: Abnormal chromosome 7 or A complex karyotype (3 or more anomalies)	-	-
Peripheral blood cytopenias [b]	0 or 1	2 or 3	-	-	-

[a] sum all 3 for overall IPSS score

[b] IPSS definition of Peripheral Blood Cytopenias: Haemoglobin < 10 g/dL, Absolute neutrophil count < 1,500/mm^3, Platelet count < 100,00/mm^3

Appendix 3
International Working Group (IWG) Response Criteria for MDS

(Cheson et al. Blood. 2006;108:419 - 425)

IWG Criteria for Response		
Category	**Original (sustained ≥ weeks)**	**Modified (sustained ≥ 4 weeks)**
CR: Marrow	< 5% blasts; no dysplasia; normal maturation of all cell lines	≤ 5% blasts; normal maturation of all cells lines
CR: Peripheral blood	Hgb ≥ 11 g/dL; ANC ≥ 1,500/mL; platelets ≥ 100,000/mL; 0% blasts; no dysplasia	Hgb ≥ 11 g/dL; ANC ≥ 1000/mL; platelets ≥ 100,000/mL; 0% blasts; hematologic improvement responses noted in addition to marrow CR
PR	Same as CR, except blasts ↓ by ≥ 50% or lower FAB	Same as CR, except blasts ↓ by ≥ 50%, still greater than 5% in marrow
IWG Criteria for Hematological Improvement		
Category	**Pretreatment**	**Modified IWG Response Criteria* (≥ 8 weeks)**
Erythroid (HI-E)	Hgb < 11 g/dL	Hgb ↑ of ≥ 1.5 g/dL
		↓ of ≥ 4 RBC transfusions/8 weeks versus pretreatment requirement in previous 8 weeks; only RBC transfusions given for a pretreatment Hgb of ≤ 9.0 g/dL count
Platelet (HI-P)	< 100,000/mL	↑ of ≥ 30,000/mL (starting with > 20,000/mL)
		↑ from < 20,000/mL to > 20,000/mL by ≥ 100%
Neutrophil (HI-N)	< 1,000/mL	↑ of ≥ 100% and > 500/μL
Progression/Relapse after hematological improvement		≥ 1 of the following: ≥ 50% decrement from maximum response levels in granulocytes or platelets; ↓ in Hgb by ≥ 1.5 g/dL; transfusion dependence