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)**

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STATISTICAL ANALYSIS PLAN

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**
STUDY DRUG:	**Epoetin beta (RO205-3859)**
VERSION NUMBER:	**2**
IND NUMBER:	**N/A**
EUDRACT NUMBER:	**N/A**
SPONSOR:	F. Hoffmann-La Roche Ltd
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DATE FINAL:	21 Jun 2019
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1. BACKGROUND

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 (Casadevall et al., 2004; Economopoulos et al., 1999; Hellstrom-Lindberg et al., 2003; Remacha et al., 1999) 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%(Casadevall et al., 2004; Hellstrom-Lindberg et al., 2003).

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.(Moyo, Lefebvre, & Duh, 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 pre-therapy 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, Montgomery, Dybedal, Porwit-MacDonald, & Hellstrom-Lindberg, 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 for rHuEpo in Myelodysplastic et al., 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 hemoglobin 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 (Hellstrom-Lindberg et al., 2003; Jadersten et al., 2008).

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 evaluate 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. 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 (Cheson et al., 2006). The trial will be conducted at approximately 7 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.

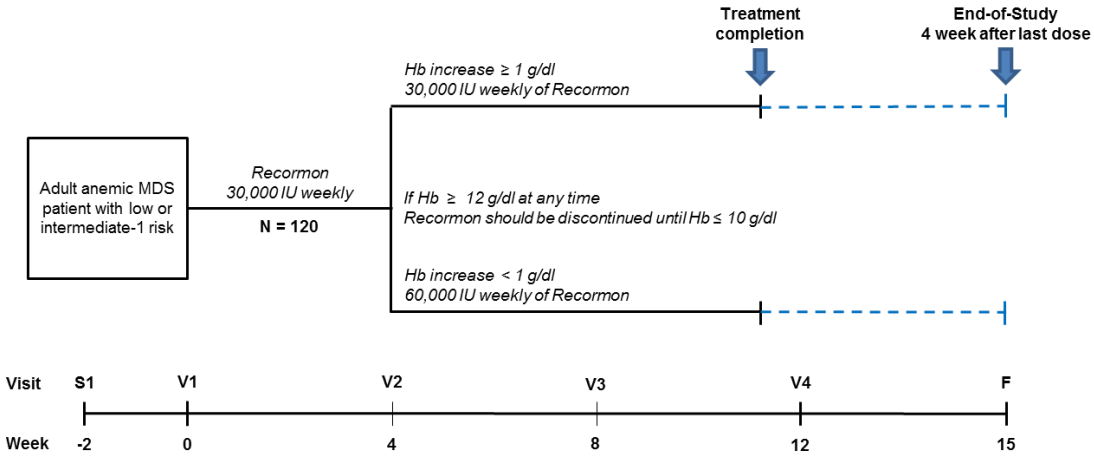


Figure 1 Study Scheme

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.

TABLE 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)

[e] 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 ≥ 12 g/dL at any time, Recormon® should be discontinued until Hb levels are ≤ 10 g/dL.

2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in Appendix 1. For additional details, see the Schedule of Assessments in Table 1

2.2 OUTCOME MEASURES

2.2.1 Efficacy Outcome Measures

The efficacy outcome measures as hematologic improvement (HI) for this study are as follows:

- The cumulative proportion of patients achieving hematologic improvement on erythroid response (HI-E) at week 12 according to IWG 2006 (Cheson et al., 2006) definition as
  - Hb increase by $\geqslant$ 1.5 g/dL or
  - 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
- Proportion of patients with hematologic improvement onplatelet response (HI-P)
  - Absolute increase of ≥ 30 x 10^9/L for patients starting with > 20 x 10^9/L platelets. Or
  - Absolute increase to Increase to > 20 x 10^9/L for patients starting with < 20 x 10^9/L and by at least $\geq$ 100%
- Proportion of patients with hematologic improvement on neutrophil response (HI-N) (At least 100% increase and an absolute increase > 0.5 x 10^9/L)

2.2.2 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- safety assessment 4 weeks after the last Recormon administration or after early withdrawal (unless the reason for early withdrawal is withdrawal of consent)

2.3 DETERMINATION OF SAMPLE SIZE

Sample size based on a 5% significance level and the 80% power with 10% drop out resulting of 100 patients in total.

- Efficacy: Assuming a 10% withdrawal rate, 100 patients will be enrolled such that we expect 90 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 90 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 0.089 (i.e. the 95% confidence interval would be 0.161 to 0.339).

- Safety: Assuming more than 90% of target patients will be administered, so we expect 100 patients will not withdraw and will remain evaluable. With 100 evaluable patients in this study, the sample size is sufficient to have at least 92% 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.

2.4 ANALYSIS TIMING

There will be 2 analysis timing defined for the study analyses: one interim and final analysis. The interim and final analysis are planned, when first 30 and 120 enrolled patients have completed their 12-week treatment, respectively.

Table 2 Example Table Format for Outlining Analysis Timings

Analysis	Timing of Analysis	Percent Information	Adjusted Two-Sided Alpha Level	Cumulative Two-Sided Alpha Level	Power (%)
First interim	30 patients	25%	0.0155	0.031	80
Final	100 patients	100%	0.025	0.05	80

3. STUDY CONDUCT

3.1 RANDOMIZATION ISSUES

This is an open-label non randomized single-arm study.

3.2 DATA MONITORING (STEERING COMMITTEE)

NA

4. STATISTICAL METHODS

Descriptive statistic would be performed using t-test and pair t-test for independent or dependent continuous variables to test significant, while chi-square or ANOVA would perform to test difference between nominal two group variables or more than 2 groups with continuous variables respectively. Univariate and multivariate logistic regression would be performed in accordance with ANCOVA in order to controlled confounding variable factors to realize adjusted mean.

All descriptive statistic would be presented as 95% confidence interval or mean and standard deviation (SD).

Demographic and baseline characteristics of efficacy and safety variable (primary and secondary endpoints) including exploratory endpoint will be summarized as table and above criteria for statistical significant would be used.

All demographic baseline summaries will base on intent-to-treat (ITT) population. Safety endpoint analysis will be presented as grade 3, 4, overall survival and adverse events

4.1 ANALYSIS POPULATIONS

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.

4.1.1 Intention to treat 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.

4.1.2 Safety Population

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

4.2 ANALYSIS OF STUDY CONDUCT

All baseline and demographic characteristics will be summarized for the ITT and safety populations for overall. Included will be age, gender, height, weight, hematologic laboratory values, and concomitant disease history. Pregnancy test results (serum test) will be summarized for women of child-bearing potential for the safety population; and blood pressure level will also be summarized as safety population.

Notes:

- Age will be calculated as the integer ((Date of Consent – Date of Birth) / 365.25). Only year of birth is collected. Day and month will be replaced with the 1st of the month and year (January) respectively. Age will be presented/summarized as a whole number. Derived age will be used in all summaries.
- Blood pressure categories were classified by JCN8 criteria (James et al., 2014) (percentages and number of patients are derived from the overall efficacy population) will be used as the cut off points for the blood pressure categories
    - For patients aged ≥ 60 years who had systolic blood pressure (SBP) < 150 mmHg and diastolic blood pressure (DBP) <90 mmHg was considered no hypertension.
    - For patients aged < 60 years who had SBP <140 mmHg and DBP <90 mmHg was considered no hypertension.
    - For patients regardless of aged who had either diabetes or chronic kidney disease (CKD), SBP < 140 mmHg and DBP <90 mmHg was considered no hypertension.

- Medical history will be coded according to the latest version of Medical Dictionary for Regulatory Activities (MedDRA).

Table. 3 Demographic data

Characteristics	**Number (Percentage)** **Mean± SD/ Median (min-max)***
Age	
Gender (Female)	
Proportion of patients who have concomitant disease (HT, DM, CKD if any)	
Proportion of patients who required transfusion**	
RBC unit required for transfusion	
Hematologic laboratory	
Hb (g/dL)	
Platelet (10^6 /µL)	
Neutrophil (10^6 /µL)	
WBC	

*where applicable

** at least 1 units prior study entry would be counted

4.3 EFFICACY ANALYSIS

Primary endpoint will be percentage of patients who achieved response based on response criteria according to IWG2006 at week 12

Secondary endpoint will be percentage of events that occurred based on NCI-CTCAE version 4.0.

4.3.1 Primary Efficacy Endpoint

Primary efficacy endpoint would be percentage of patients who achieved response based on response criteria according to IWG2006 which were

- An increasing of Hb of ≥1.5 g/dL at week 12.

Statistical significant of base line and treatment at week 12 as adjusted mean would be performed using multivariate logistic regression. Covariate variables such as age, gender, hypertension categories would be controlled as confounding factors using ANCOVA.

Pairwise dependent t-test using continuous variables (percentage of response patients) would be performed to test statistical significant at type I error of 0.05.

Analysis will be based on pool data, stratified by centers were not pre-specified and would not be included in primary analysis.

4.3.2 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 or 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.

The secondary efficacy endpoint would be presented as percentage of patients who achieved above platelet or neutrophil response criteria

Statistical significant by type I error (α) level would be 0.05. statistical significant difference would be tested using dependent pair t-test in which covariate, e.g., age, gender, hypertension categories was controlled by ANCOVA method.

Table. 4 Hematologic improvement (HI)

Response	Number	Percentage
Hematologic responses		
Platelet response		
Neutrophil response		

4.3.3 Sensitivity Analyses

N/A

4.3.4 Subgroup Analyses

Not currently planned

4.4 SAFETY ANALYSES

Safety analysis would be performed by collecting samples for laboratory test by study site's local laboratory for analysis prior to Recormon® administration and at the end of study. Any adverse events which considered related or non-related must be reported as descriptive statistics (frequencies versus total patients) categorized by major organ functions. The following variables would be analyzed for safety endpoints at the end of study period comparing with baseline.

- Hematologic laboratories; CBC, WBC and differentials and platelet count, ferritin level
- Liver function: serum creatinine alanine aminotransferase (ALT/SGPT) and aspartate aminotransferase (AST/SGOT) in all patients.
- Kidney function : creatinine level
- Cardiovascular disease : blood pressure level
- Changes in concomitant medication (if any)

All safety data would be reported based on organ function both total adverse event (AE) and serious adverse event (SAE).

Table. 5 Adverse event and serious adverse events by sites of organ (HI)

Organ site of adverse event	AEs		SAEs	
	no.	%	no.	%
Blood and lymphatic system disorders				
Gastrointestinal disorders				
Vascular disorders				
Infections and infestations				
Psychiatric disorders				
Skin and subcutaneous tissue disorders				
Eye disorders				
Cardiac disorders				

Table. 6 Changes in laboratory values

Laboratory	Screening (Mean±SD)	Week 12 (Mean±SD)	P-values
Hematologic : CBC, WBC, Neutrophil, Platelet, Hb			
Liver : SGOT, SGPT			
Kidney ; creatinine			
Etc.			

*pair t-test : $p<0.05$ considered significant, CBC = completed blood count, WBC= white blood cell, Hb= Hemoglobin level, SGOT=Serum glutamic oxaloacetic transaminase, SGPT=serum glutamic-pyruvic transaminase.

Descriptive statistic would be applied for safety analysis. All safety variables would be tested for significant level using type I error of 5% (α level =0.05). Pair t-test would be performed to test significant with all above safety variables. Chi-square test or Fisher's exact would be performed for frequency tables (if any), where appropriate statistical assumption based on statistical test applied.

4.5 MISSING DATA

All key efficacy and safety variables of missing data would be verified with study site; and in case that data verification was available, double verification with central CRO and study site coordinators would accomplished. In case of no variables could be achieved, missing data would be treated by imputing method using bootstrap technique.

4.6 INTERIM ANALYSES

- The interim analysis was planned once thirtieth patients finished study at week 12; and patients deposition diagram based on screening, dosage adjustment and responses would be also demonstrated. (Figure.2) The interim efficacy for primary or secondary endpoint including safety analysis would be performed based on analysis methodology in section 4.3.1 and statistical assumption in table 2.

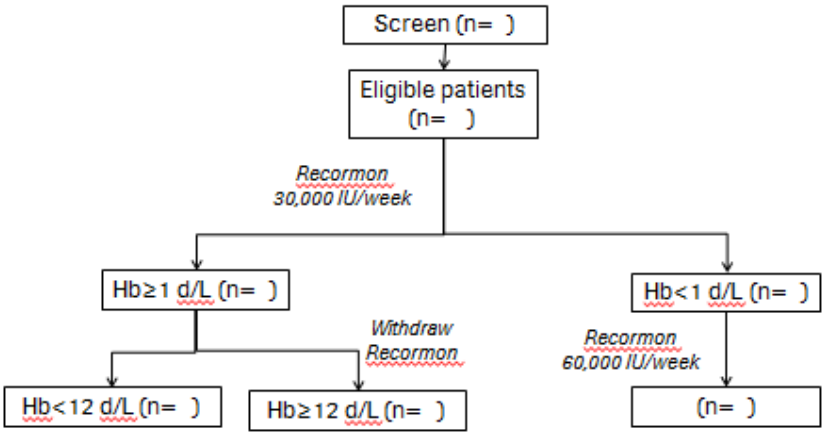


Figure 2 patients deposition diagram

An interim analysis would base on early stopping rule by Simon two stages(Cornelia & Meinhard, 2011), (Appendix 3)

Appendix 1
Protocol Synopsis

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:	1
EUDRACT NUMBER:	To be determined
IND NUMBER:	To be determined
TEST PRODUCT:	**epoetin beta** (RO205-3859)
PHASE:	IV
INDICATION:	**Treatment of symptomatic anemia associated with Myelodysplastic Syndromes (MDS)**
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives

Primary Objectives

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

Secondary Objectives

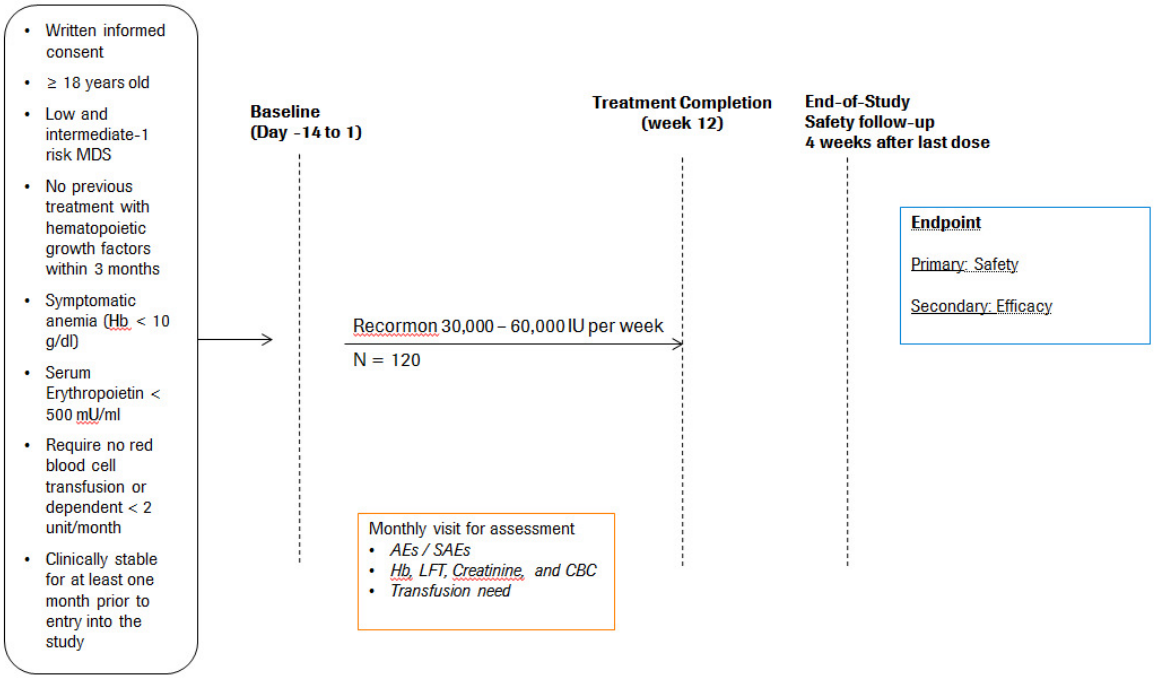
To assess the efficacy of Recormon for treating anemic patients with low/intermediate 1 risk MDS

Study Design

The study consists of a 2-week baseline phase, a 12-week treatment phase and end-of-study visit (see figure). 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 (see Investigational Medicinal Products part).
At baseline, serum levels of endogenous erythropoietin are assessed, as well as liver and kidney function. Bone marrow morphology analysis and karyotyping are also performed at baseline if they have not been assessed in the 6 months prior to participation in the study. Complete blood count is performed at baseline and every 4 weeks until the end of the 12-week period.

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 in case of: (a) severe adverse reaction or severe intercurrent illness; (b) a request by the patient or by the investigator; and (c) evolution into high-risk MDS or overt leukemia.



Number of Patients

120 patients expected to be enrolled.

Target Population

Adult anemic MDS patients (≥18 years old) in the low and intermediate 1 risk group according tothe International Prognostic Scoring System (IPSS).

Inclusion Criteria

- Written informed consent
- Adult patients (≥ 18 years old)
- Low and intermediate-1 risk MDS (having IPSS risk score ≤ 1) confirmed with bone marrow morphology analysis and karyotyping within 6 months prior to participation in the study
- No previous treatment with hematopoietic growth factors within 3 months prior to study entry
- Symptomatic anemia (Hb < 10 g/dl)
- Serum Erythropoietin < 500 mU/ml
- Require no red blood cell transfusion or dependent on < 2 units/month
- Clinically stable for at least one month prior to entry into the study

Exclusion Criteria

- Contraindications to Recormon treatment, Hypersensitivity to the active substance or any of the excipients
  - Poorly controlled hypertension
- History of Acute myeloid leukemia (AML) or high risk for AML
- Pregnancy or breast-feeding
- Women of childbearing potential without effective contraception
- 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

Procedures (summary)

Enrolment

All potential study patients must provide signed written informed consent before undergoing any study specific procedure.

Women of childbearing potential had to agree to use two reliable forms of contraception simultaneously or to practice complete sexual abstinence.

Baseline (Day -14 to Day 1)

Patients will undergo the following assessments within 14 days prior to enrolment into the study, unless the procedure/assessment has already been conducted during this time period as part of the patient's routine clinical care:

- Demographics, medical history, and concomitant medications
- General physical examination, height, weight, measurement of vital signs (including blood pressure, pulse, and body temperature)
- Laboratory examination: Hemoglobin (Hb), Serum erythropoietin (EPO), Liver function tests (LFTs), Creatinine, Serum Ferritin, and Complete blood count (CBC)
- Transfusion need

12-week treatment phase

Patients will see the doctor every 4 weeks until 12 weeks. At each visit the patients will undergo the following examinations:

- Assessment of any AEs / SAEs + relevant concomitant medication
- Physicsal examination
- Laboratory examination: Hb, LFT, Creatinine, and CBC
- Transfusion need

End-of-study visit

4 weeks after last administration of study drug (week 12) or after early withdrawal (unless the reason for early withdrawal is withdrawal of consent), all enrolled patients will undergo the following assessments at a post-treatment safety follow-up visit:

- Assessment of any AEs / SAEs
- Physical examinatioin
- Laboratory examination: Hb, LFT, Creatinine, and CBC, Serum Ferritin
- Transfusion need
- Concomitant medication

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.

Length of Study

Safety Outcome Measures

Efficacy Outcome Measures

The cumulative proportion of patients achieving erythroid response at week 12.

Erythroid response was defined according to IWG 2006 definition as

- Hb increase by ≥ 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 pretreatment transfusion number in the previous 8 weeks. Only RBC transfusions given for a Hgb of ≤ 9.0 g/dL pretreatment will count in the RBC transfusion response evaluation

Investigational Medicinal Products

Appendix 2
Schedule of Assessments

	Baseline	**treatment phase**				**End-of-Study visit***
Visit	**S1**	**V1**	**V2**	**V3**	**V4**	**F**
Week	**-2**	**0**	**4**	**8**	**12**	**16***
Visit window ± (week)			**1**	**1**	**1**	**1**
Informed consent	X					
Medical history	X					
Physical examination	X	X	X	X	X	X
CBC	X	X	X	X	X	X
Liver function test	X	X	X	X	X	X
Creatinine	X	X	X	X	X	X
Serum EPO	X					
Serum Ferritin	X					X
Transfusion needed	X	X	X	X	X	X
Concomitant treatment	X	X	X	X	X	X
Adverse event		X	X	X	X	X
Drug administration**		X	X	X	X	
Treatment adjustment			X			

Appendix 3
Statistical Analysis Method

1. The analysis of this study will be conducted using STATA 13 software (STATA CORP); and both early stopping rule and hypothesis testing for different will also be implemented as followings.

2. The early stopping rule by simon two stage design for observational study will be implemented. An assumption based on sample size calculation (section 2.3) will be used as followings,

    - The response rate of epoetin beta should be more than 25%, whereas the response rate of best supportive care would be 7%.

    - The type I error was 5% with 80% power (type II error) to detect the differences

A design is indexed by four values r1/n1 r/n ; and the study would be stopped if there were $\leq$ r1 responders out of the first n1 participants. The null hypothesis would be rejected if there were > r responders out of n participants.

While R(p) was the probability of concluding that there were no evidence of a treatment effects and EN(p) was the expected sample size

Type I error = .05, Power = .8

H_0: p = p0

H_1: p = p1 >=p0, where p0 is .07 and p1 is .25

The study is stopped if there are <= r1 responders out of the first n1 participants. The null hypothesis is rejected if there are >r responders out of n participants

So, the treatment would be stopped if alternative hypothesis (Ha $\geq$ 0.25) were rejected. The minimax and the optimal design which demonstrates the minimal and optimal number of patients to detect the efficacy was used(Cornelia & Meinhard, 2011).

3. The hypothesis testing of response rate in this study compared to baseline assumption which were 0.25 would also performed using chi-square test as followings

H_0: p1 =0.25

H_1: p1 ≠ 0.25 by chi-square test, where α =0.05

The hypothesis H0 would be rejected if p value by chi square test < 0.05 which indicate the response of intervention in this study was different from hypothesis

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