A Phase 2, Randomized, Open-Label, Parallel, Comparative, Dose-Finding Study to Evaluate the Efficacy and Safety of AMG531 in Aplastic Anemia Subjects with Thrombocytopenia Refractory to Immunosuppressive Therapy

Protocol

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AA	Aplastic Anemia
ADR	Adverse Drug Reaction
AE	Adverse Event
ALB	Albumin
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AML	Acute myelogenous leukemia
APTT	Activated partial thromboplastin time
[redacted]	[redacted]
AST	Aspartate aminotransferase
ATG	Anti-thymocyte globulin
AUC_{0-t}	Area under the serum concentration-time curve from time 0 to the last detectable time
BUN	Blood urea nitrogen
CI	Confidence Interval
[redacted]	[redacted]
C_{max}	Maximum serum concentration
CMML	Chronic myelomonocytic leukemia
Cr	Creatinine
CTCAE	Common Terminology Criteria for Adverse Events
D-Bil	Direct bilirubin
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
FAS	Full Analysis Set
γ-GTP	γ-glutamyl transpeptidase
GCP	Good Clinical Practice, international standards for conducting clinical studies.
G-CSF	Granulocyte-colony stimulating factor
GPI-cell	Glycosyl phosphatidyl inositol-cell
Hb	Hemoglobin
[redacted]	[redacted]
Ht	Hematocrit
ICF	Informed Consent Form
IFN- γ	Interferon- γ
IST	Immunosuppressive therapy
ITP	Idiopathic (Immune) Thrombocytopenic Purpura
IRB	Institutional review board
IWRS	Interactive Web Response System
LIN	Lineage
LDH	Lactate dehydrogenase
NYHA	New York Heart Association
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration

ABBREVIATION	DEFINITION
MCV	Mean corpuscular volume
MDS	Myelodysplastic syndromes
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PNH	Paroxysmal nocturnal hemoglobinuria
PPS	Per Protocol Set
PS	Performance status
PT-INR	Prothrombin time - International Normalized Ratio
PTs	Preferred Terms
RBC	Red blood cell
Ret	Reticulocyte
SDP	Single Donor Platelet
SID	Subject identification
SOC	System Organ Class
T-Bil	Total bilirubin
T-Cho	Total cholesterol
TIBC	Total iron-binding capacity
TMP	Thrombopoietin mimetic peptide
TNF- α	Tumor necrosis factor- α
T_{max}	Time to reach maximum serum drug concentration
TP	Total protein
TPO	Thrombopoietin
TSAT	Transferrin saturation : TSAT=Fe×100/TIBC
UA	Uric acid
UIBC	Unsaturated iron-binding capacity
WBC	White blood cell

DEFINITION OF TERMS

Platelet Response

Platelet response is defined as (1) Absolute increase of $\geq 20x10^9$/L above baseline or, (2) Increase to $\geq 10x10^9$/L and by at least 100% from baseline.

Erythroid Response

Erythroid response is defined in those who with a pretreatment hemoglobin of < 9.0 g/dL as an increase in hemoglobin concentration of ≥ 1.5 g/dL above baseline without transfusion, or reduction in the transfusion unit by at least 4 units for 8 consecutive weeks compared with the pretreatment transfusion requirement in the previous 8 weeks prior to the first administration of AMG531 (Day -55 to Day 1).

Neutrophil Response

Neutrophil response is defined in those with a pretreatment absolute neutrophil count (ANC) of $< 0.5x10^9$/L as a 100% increase over the baseline, or an increase in ANC of $> 0.5x10^9$/L in subjects with a pretreatment ANC of $< 1.0x10^9$/L.

Baseline

Baseline values are defined as the values obtained before dosing AMG531 on Study Day 1. Data obtained during the screening period will serve as baseline values for those not measured or reported on Study Day 1. If multiple evaluations are performed during the screening period for a particular test, with the exception of platelet count, the values measured closest to the first administration of AMG531 will be considered as the baseline values (if hemoglobin concentration at Study Day 1 is within 28 days after RBC transfusion, hemoglobin concentration determined during the screening period will be used as baseline hemoglobin).

Baseline Platelet Count

Baseline platelet count is defined as the mean of two lowest platelet counts measured in 8 weeks prior to enrollment. Platelet count that is obtained within 7 days after platelet transfusion will not be used. The baseline platelet according to the definition of protocol Master Ver1.1 (The mean of two lowest platelet counts measured in 8 weeks prior to enrollment. Platelet count that is obtained within 3 days after platelet transfusion will not be used.) will be also collected .

Platelet Transfusion

Platelet transfusion given due to platelet count of $< 10x10^9/L$ (prophylactic transfusion) or due to bleeding (therapeutic transfusion).

RBC Transfusion

RBC transfusion given due to the hemoglobin concentration of ≤ 9.0 g/dL or due to symptomatic anemia

Adverse Drug Reaction

Adverse events of which causal relationship to the investigational product cannot be ruled out (any events assessed to be other than "unlikely" or "not related").

Study Duration

Study duration of each subject in this study is specified as the period from the day of obtaining written informed consent through the end of examinations on completion of treatment (or withdrawal).

Observation and Examination Period

In this study, Week 1 (Day 1) is defined to be the day of initial administration of AMG531. Initial dose evaluation period is defined to be the period from Week 1 to Week 8, Extension period is the period from Week 9 to Week 52, and Long-term treatment period is the period from Week 53 to Week 156.

Aplastic Anemia with Refractory Thrombocytopenia

Aplastic anemia with thrombocytopenia defined as platelet count of $\leq 30x10^9/L$ that does not respond to the immunosuppressive therapy (ATG + cyclosporine), or relapsed after having showed response.

Transfusion Independence

Achieving platelet or RBC transfusion free period of at least 8 consecutive weeks.

Tri-lineage response

Tri-lineage response is defined in those achieving platelet response, erythroid response, and neutrophil response all together.

Normal level

Normal level is defined as platelet counts >$50x10^9$/L, hemoglobin concentration >10.0 g/dL, and neutrophil counts >$1.0x10^9$/L

Stable response

Stable response is defined as platelet counts ≥$30x10^9$/L, hemoglobin concentration ≥9.0 g/dL, and neutrophil counts ≥$0.5x10^9$/L maintained during dose tapering or discontinuation without transfusion

Cytogenetic abnormality

Any cytogenetic abnormalities newly emerged during or after the initiation of AMG531 treatment

PROTOCOL SYNOPSIS

I TITLE

A phase 2, Randomized, Open-Label, Parallel, Comparative, Dose-Finding Study to Evaluate the Efficacy and Safety of AMG531 in Aplastic Anemia (AA) Subjects with Thrombocytopenia Refractory to Immunosuppressive Therapy

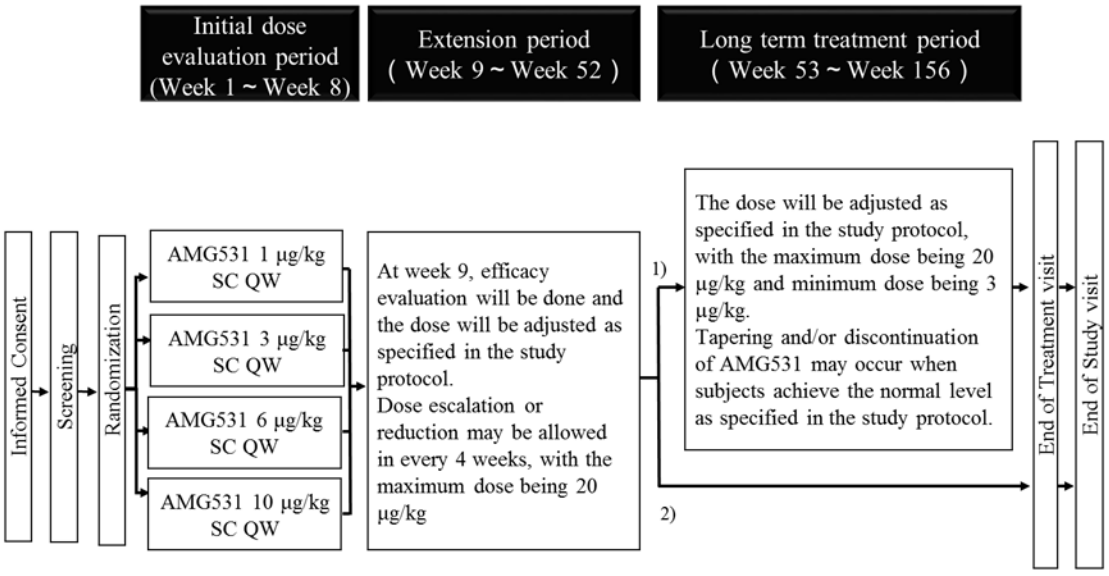
II STUDY OBJECTIVES

The present study will be conducted to evaluate the efficacy and safety of AMG531 and to determine the recommended initial dose of AMG531 on the basis of its efficacy and safety when it is administered SC, QW at a dose of 1, 3, 6 or 10 μg/kg to the aplastic anemia patients with immunosuppressive-therapy refractory thrombocytopenia and also to assess the pharmacokinetics of this product during the initial dose evaluation period. Its efficacy and safety during the extension period will also be evaluated. Efficacy and safety of AMG531 in the long term treatment beyond 1-year will be further evaluated for those showing continuous responses after 1 year treatment.

III STUDY DESIGN

This is a multi-center, randomized, open-label, parallel, comparative, dose-finding study.

The overall study design is presented below.



1) Subjects who meet the criteria specified in section 5.4 move to Long-term treatment period
2) Subjects who don't meet the criteria specified in section 5.4 move to End of treatment.

IV STUDY SUBJECTS

AA subjects with thrombocytopenia refractory to immunosuppressive agents.

IV-1 Inclusion criteria

Subjects may be included in the study if they meet all of the following criteria:

1) Patients who have provided written informed consent of their free will to participate in this clinical study. Written informed consent must be obtained prior to performing any study-related procedure
2) The subject is able and willing to comply with study procedures and follow-up as described in the protocol and ICF
3) Males and female subjects ≥ 19 years of age at the time of obtaining informed consent
4) Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of ≤ 2 at the time of screening
5) Diagnosis of AA, confirmed by bone marrow and cytogenetic studies
6) Patient who is refractory to immunosuppressive therapy (IST)
7) Prior treatment with at least one course of horse or rabbit anti-thymocyte globulin (ATG) with cyclosporine
8) Thrombocytopenia defined as platelet $\leq 30 \times 10^9$/L
9) Fulfilling all of the following criteria in the screening examination
    - T-Bilirubin ≤ 1.5 times the upper limit of the laboratory normal range
    - ALT and AST ≤ 3 times the upper limit of the laboratory normal range
    - Creatinine ≤ 2.0 mg/dL

IV-2 Exclusion criteria

Subjects must be excluded from participating in this study if they meet any of the following criteria:

1) Concurrent active infection not adequately responding to appropriate therapy
2) Human immunodeficiency virus positivity
3) Bone marrow reticulin grade of > 1 (Appendix 1)
4) Previous or concurrent active malignancies other than localized tumors diagnosed more than one year previously and treated surgically with curative intent (basal cell carcinoma or surgically resected in situ carcinoma of the cervix with apparent success ≥ 12 months prior to enrollment, as well as other cancers which have not been treated or have remained disease-free for at least 3 years before enrollment are eligible)
5) Clinically significant cardiac disease (class III or IV of the New York Heart Association (NYHA) classification; unstable angina pectoris; myocardial infarction

within 6 months or is post angioplasty or stenting within 6 months; uncontrolled hypertension; clinically significant cardiac arrhythmia)

6) Arterial or venous thrombosis within the last 1 year before enrollment
7) Other cause of thrombocytopenia (for instance MDS, ITP, liver cirrhosis)
8) Subjects with AML or CMML
9) AA with hemolytic predominant PNH (hemolytic predominant is defined as LDH > 1.5 times the upper limit of the laboratory normal range)
10) Uncontrolled diabetes
11) Receiving other investigational agents within 16 weeks before starting the study treatment
12) Receiving any agent used to treat AA, including ATG or ATG + cyclosporine within 6 months before starting study treatment and/or cyclosporine or anabolic hormone within 6 weeks before starting the study treatment
13) History of PEG-rHuMGDF, recombinant human thrombopoietin, AMG531, and other TPO-receptor agonist
14) Who plans to conduct hematopoietic stem cell transplantation within 1 year
15) Known hypersensitivity to any recombinant *E. Coli* derived product
16) Female subjects who are nursing or pregnant or are unwilling to take oral contraceptives or refrain from pregnancy if of childbearing potential
17) Subjects who are considered to be ineligible for the study by the investigator for reasons other than the above

V DOSE, DOSING SCHEDULE, AND TREATMENT DURATION

There must be at least 3 days between the doses of AMG531 in each subject.

V-1 Initial dose evaluation period (Week 1 to Week 8)

AMG531 will be administered at a dose of 1, 3, 6 or 10 μg/kg SC QW for 8 weeks. Dose adjustment (either escalation or reduction) will not be allowed during the initial dose evaluation period except for the cases defined in the V-4 Criteria for discontinuing and resuming study treatment.

V-2 Extension period (Week 9 to Week 52)

Initial dose of AMG531 for the extension period will be decided based on the efficacy and safety data observed during the initial dose evaluation period. If a subject does not show a platelet response at Week 9, the dose will be increased by one level according to Table V-1. AMG531 dose adjustment (extension period) table. If no platelet measurement is available due to the platelet transfusion, then that week's platelet response is considered as having no response.

1) Dose escalation

Dose escalation will be allowed during the extension period. If a subject does not show a platelet response after 4-week treatment with AMG531 at the previously escalated dose, the dose may be further increased by one level according to Table V-1 at the discretion of the investigator, with the highest dose being 20 µg/kg. The necessity and timing of dose escalation after 4 week administration at a previously escalated dose will be decided by investigator after thorough consideration of the relevant safety and efficacy data for each subject.

2) Dose adjustment

If a subject shows a platelet response, the dose may be adjusted as appropriate to maintain the platelet response at the discretion of the investigator referring to the relevant efficacy and safety data of the each subject. For each dose adjustment, dose may be increased or decreased only by one level at a time according to the Table V-1, with the highest dose being 20 µg/kg.

Table V-1 AMG531 Dose adjustment table (extension period)

AMG531 Dose
1 µg/kg
3 µg/kg
6 µg/kg
10 µg/kg
13 µg/kg
16 µg/kg
20 µg/kg

V-3 Long-term treatment period (Week 53 to Week 156)

1) Initial Dose

AMG531 will be administered SC QW at the same dose received as the last dose in the extension period. If dose adjustment is deemed to be necessary at Week 53 by investigator, the dose may be adjusted according to the Table V-2 Dose adjustment (long-term treatment period) table.

2) Dose adjustment

The dose may be adjusted as appropriate to maintain the platelet response at the discretion of the investigator. For each dose adjustment, dose may be increased or decreased only by one level at a time according to the Table V-2, with the highest dose being 20 µg/kg and the lowest dose being 3 µg/kg.

Table V-2 AMG531 Dose adjustment (long-term treatment period)

AMG531 Dose
3 µg/kg
6 µg/kg
10 µg/kg
13 µg/kg
16 µg/kg
20 µg/kg

3) Tapering and Discontinuation

If tri-lineage is maintained within normal level for 8-consecutive weeks with the same dose without transfusion, the dose will be decreased by one level at every 4 weeks. If tri-lineage is maintained within normal level for 4 consecutive weeks with 3 µg/kg without transfusion, AMG531 will be discontinued.

Normal level is defined as platelet counts $>50\times10^9$/L and hemoglobin concentration >10.0 g/dL and neutrophil counts $>1.0\times10^9$/L.

While tapering, if platelet counts drop to less than 30×10^9/L, hemoglobin to less than 9.0 g/dL, or neutrophil counts to less than 0.5×10^9/L, the tapering has to be stopped and dose will be adjusted following section V-3 2). If the study drug were discontinued, it will be resumed at a dose of 3 µg/kg and further adjusted in accordance with section V-3 2). Tapering may be tried again at the discretion of investigator.

While tapering, if patient does not meet the criteria of further tapering but maintains steady stable response, the dose will be kept stable. During tapering, dose reduction should follow section V-3 3), not V-3 2). While discontinuation, if patient maintains the steady stable response, dosing will not be resumed.

V-4 Criteria for discontinuing and resuming study treatment

If the platelet has exceeded $400x10^9$/L during the treatment period, study treatment will be temporarily discontinued. Once the platelet count falls to $< 200x10^9$/L, administration of AMG531 will resume at a reduced dose by one level according to the protocol. Once the platelet count falls to $\leq 50x10^9$/L during the treatment with reduced dose by one level, dosing will be resumed at the temporarily discontinued dose.

If the platelet has exceeded $200x10^9$/L during the treatment period, the dose of AMG531 will be reduced to the next lower dose tested. If the temporarily discontinued dose is 1 µg/kg, treatment will be resumed at the dose of 1 µg/kg.

Other than the reasons above, investigator can reduce the dose at any time during the study if safety concerns arise.

VI STUDY ENDPOINTS

VI-1 Efficacy

1) Primary endpoint

The proportion of subjects achieving a platelet response at Week 9.

2) Secondary endpoints

- The proportion of subjects achieving a platelet response any time during the initial dose evaluation period, Week1 through Week 12, Week 1 through Week 16, Week 1 through Week 24, and Week 1 through Week 52
- The proportion of subjects who become platelet transfusion independent during the initial dose evaluation period, Week1 through Week 12, Week 1 through Week 16, Week 1 through Week 24, Week 1 through Week 52, Week 1 through Week 104, and Week1 through Week 156
- The proportion of subjects achieving erythroid response and/or neutrophil response during the initial dose evaluation period, Week1 through Week 12, Week 1 through Week 16, Week 1 through Week 24, Week 1 through Week 52, Week 1 through Week 104, and Week1 through Week 156
- Duration of platelet response
- Time to platelet response
- Changes in platelet count, hemoglobin concentration, and neutrophil count as continuous variables
- Changes in bone marrow cellularity and reticulin grade
- Changes in GIMEMA bleeding scale
- The proportion of subjects achieving tri-lineage responses
- The proportion of subjects able to discontinue study drugs after achieving normal level for 8 consecutive weeks without transfusion.
- Duration of study drug discontinuation while maintaining stable response

VI-2 Pharmacokinetics

- Serum AMG531 concentration
- Pharmacokinetic parameters

VI-3 Safety

- Adverse events
- Antibody formation against AMG531 and TPO

VI-4 Exploratory

- The changes of primitive hematopoietic stem and progenitor cells
- The changes of progenitor cell pool (colony forming cell assay)
- The changes of stromal cell (colony forming unit fibroblast assay)
- Cytokine assay (IL-2, IL-6, IL-10, IL-12, IL-17, IFN-γ, TNF-α)

VII CRITERIA FOR SUBJECT WITHDRAWAL

Any of the following circumstances will result in the subject being withdrawn from the study:

1) The subject is found to be ineligible for participation in this study due to violations in the inclusion or exclusion criteria specified in the study protocol;
2) The subject decides to discontinue his/her participation in the study;
3) The subject becomes unable to undergo necessary observations or examinations;
4) The subject who does not achieve a platelet response after 8-week treatment with AMG531 20 μg/kg QW;
5) The investigator considers that the subject should be withdrawn from the study due to an adverse event (including progression of the primary disease);
6) The subject received any of the prohibited concomitant medications or treatments;
7) The subject becomes pregnant or wants to have children during the study;
8) The investigator assesses that the subject needs to be withdrawn from the study for any reason not specified above;
9) The subject who does not meet the entry criteria for long-term treatment period

VIII TARGET SAMPLE SIZE

1) Efficacy and Safety

Eight in each cohort, a total of 32 subjects receiving AMG531 at a dose of 1, 3, 6 or 10 μg/kg during the initial dose evaluation period will be assessed for the primary endpoint.

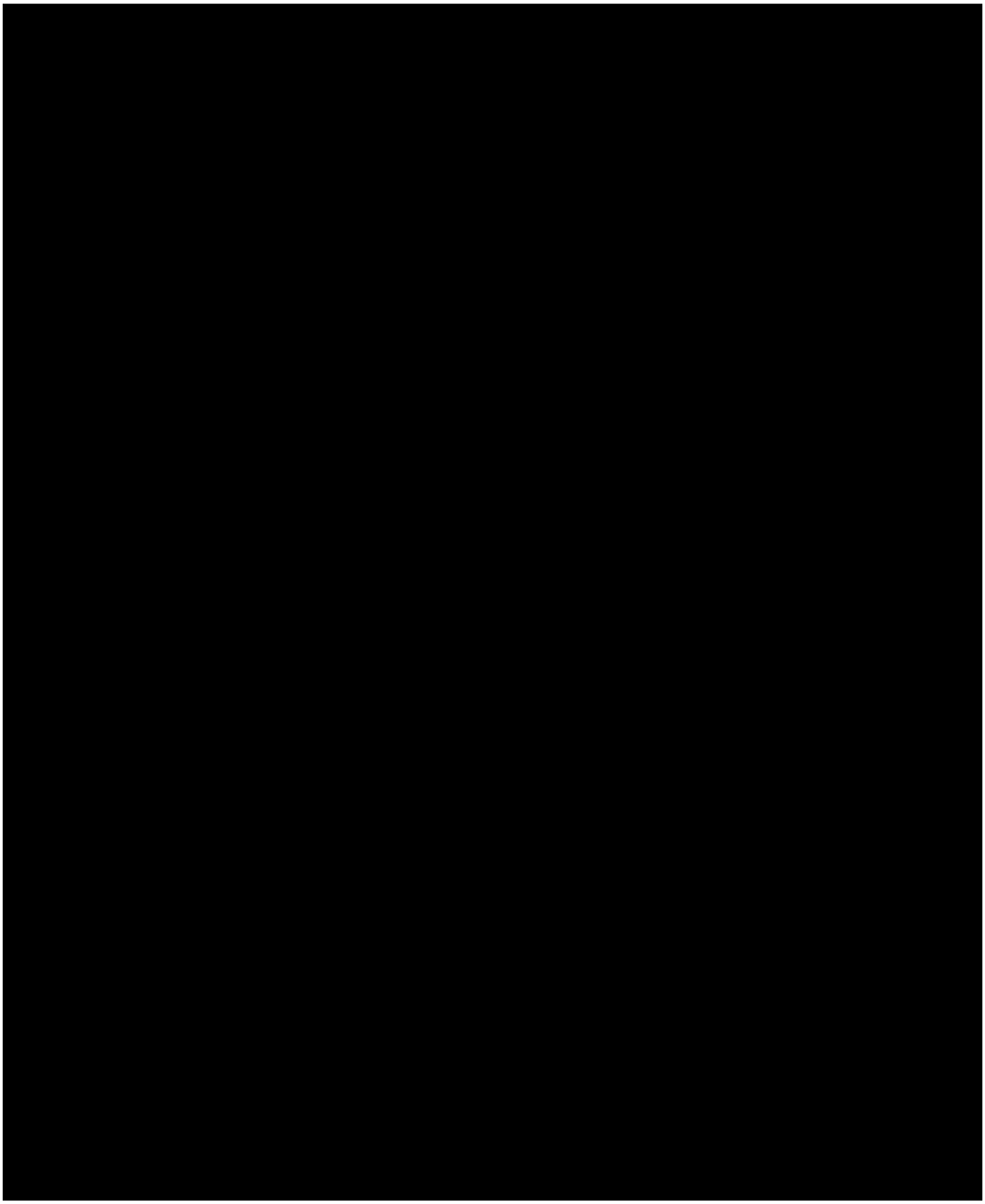
2) Pharmacokinetics

Serum concentrations of AMG531 will be determined in 3 subjects in each cohort, a total of 12 subjects (in chronological order of enrollment) receiving AMG531 at a dose of 1, 3, 6 or 10 μg/kg.

IX PLANNED STUDY PERIOD

January 2014 to March 2018

1 BACKGROUND AND STUDY RATIONALE



2 STUDY OBJECTIVES

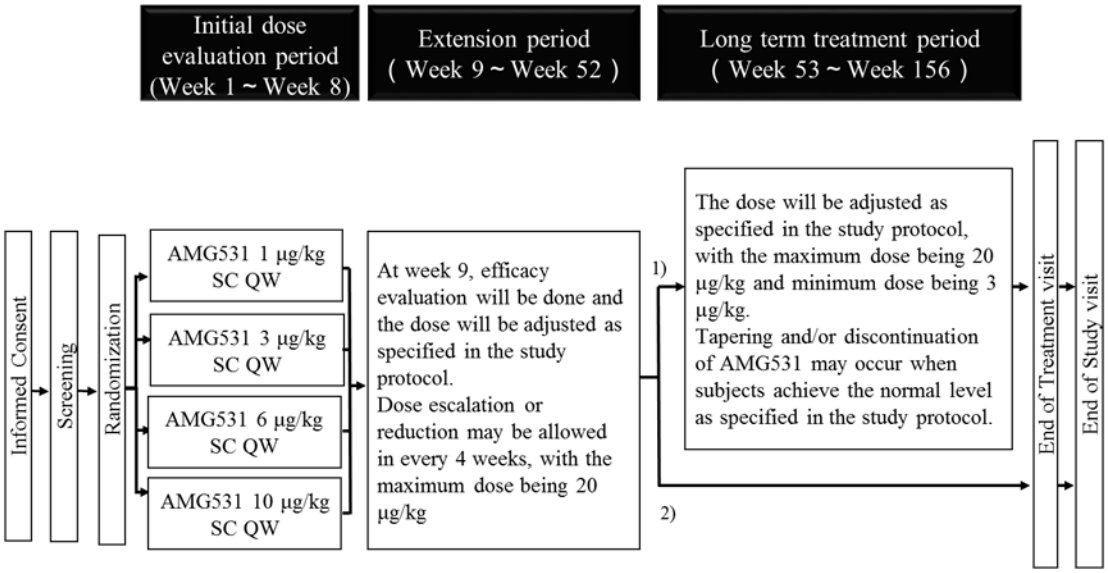
The present study will be conducted to evaluate the efficacy and safety of AMG531 and to determine the recommended dose of AMG531 on the basis of its efficacy and safety when it is administered SC, QW at a dose of 1, 3, 6 or 10 μg/kg to the AA patients with immunosuppressive-therapy refractory thrombocytopenia and also to assess the pharmacokinetics of this product during the initial dose evaluation period. Its efficacy and safety during the extended period will also be evaluated. [redacted] Efficacy and safety of AMG531 in the long term treatment beyond 1-year will be further evaluated for those showing continuous responses after 1 year treatment.

3 STUDY DESIGN

3.1 Study design

This is a multi-center, randomized, open-label, parallel, comparative, dose-finding study.

The overall study design is presented below.



1) Subjects who meet the criteria specified in section 5.4 move to Long-term treatment period
2) Subjects who don't meet the criteria specified in section 5.4 move to End of treatment.

3.2 Study phase

Phase 2

3.3 Study endpoints

3.3.1 Efficacy

3.3.1.1 Primary endpoint

The proportion of subjects achieving a platelet response at Week 9

3.3.1.2 Secondary endpoints

- The proportion of subjects achieving a platelet response any time during the initial dose evaluation period, Week1 through Week 12, Week 1 through Week 16, Week 1 through Week 24, and Week 1 through Week 52.
- The proportion of subjects who become platelet transfusion independent during the initial dose evaluation period, Week1 through Week 12, Week 1 through Week 16, Week 1 through Week 24, Week 1 through Week 52, Week 1 through Week 104, and Week1 through Week 156
- The proportion of subjects achieving erythroid response and/or neutrophil response during the initial dose evaluation period, Week1 through Week 12, Week 1 through Week 16, Week 1 through Week 24, Week 1 through Week 52, Week 1 through Week 104, and Week1 through Week 156
- Duration of platelet response
- Time to platelet response
- Changes in platelet count, hemoglobin concentration, and neutrophil count as continuous variables
- Changes in bone marrow cellularity and reticulin grade
- Changes in GIMEMA bleeding scale
- The proportion of subjects achieving tri-lineage responses
- The proportion of subjects able to discontinue study drugs after achieving normal level for 8 consecutive weeks without transfusion.
- Duration of study drug discontinuation while maintaining stable response

3.3.2 Pharmacokinetics

- Serum AMG531 concentration
- Pharmacokinetic parameters

3.3.3 Safety

- Adverse events
- Antibody formation against AMG531 and TPO

3.3.4 Exploratory

- The changes of primitive hematopoietic stem and progenitor cells
- The changes of progenitor cell pool (colony forming cell assay)
- The changes of stromal cell (colony forming unit fibroblast assay)
- Cytokine assay (IL-2, IL-6, IL-10, IL-12, IL-17, IFN-γ, TNF-α)

3.4 Randomization

Subjects assessed to be eligible for the study will be randomized to either of the four dose groups (1, 3, 6, or 10 μg/kg) according to a static allocation procedure using the baseline platelet count (platelet $\leq 10x10^9$/L or $10x10^9$/L < platelet $\leq 30x10^9$/L). A written procedure for randomization will be created and the details will be specified in it.

3.5 Target sample size

3.5.1 Efficacy and Safety

Eight in each cohort, a total of 32 subjects receiving AMG531 at a doses of 1, 3, 6 or 10 μg/kg during the initial dose evaluation period will be assessed for the primary endpoint.

3.5.2 Pharmacokinetics

Serum concentrations of AMG531 will be determined in 3 in each cohort, a total of 12 subjects (in chronological order of enrollment) receiving AMG531 at a doses of 1, 3, 6 or 10 μg/kg.

4 INVESTIGATIONAL PRODUCT

4.1 Investigational product

1) Investigational Product: AMG531
2) Generic Name: Romiplostim
3) Content and Dosage Form: AMG531 is supplied in a single use glass vial as a sterile, white, preservative free, lyophilized powder. After reconstitution with 0.72 mL of sterile water for injection, AMG531 is available at a concentration of 0.5 mg/mL.

4.2 Labeling and packaging

4.2.1 Packaging

Each box contains 10 vials.

4.2.2 Labeling

Each label displays the following information. Color of outer carton and vial labels are designated to be white.

4.2.2.1 Label for outer cartons

Statements of "For clinical trial use only" and "Cannot be used for any other purposes except for clinical trial", name and address of the IND holder, name of investigational product, batch number, expiration date and storage directions.

4.2.2.2 Label for vials

Statements of "For clinical trial use only", name of investigational product and batch number, expiration date, and IND holder name.

4.3 Storage

To be stored at 2 to 8°C and protected from light.

4.4 Dispensing, storage, control and collection of investigational product

The sponsor will provide each investigative site with the investigational product after execution of the clinical study agreement. The sponsor will develop a written procedure for controlling the investigational product and deliver it to each investigative site.

The investigational product manager at each investigative site will properly store and control the investigational product according to the procedure, and will maintain records of the inventory, dispensing and return. He/she will properly check the quantity of the investigational product against the investigational product management record. In principle, the investigational product manager will return unused vials to the sponsor after study completion or at the delivery of a new batch. Partially used and empty vials will be destroyed at the site per site's standard procedures.

The investigational product manager will submit a copy of the investigational product management record to the sponsor after study completion.

5 SELECTION OF SUBJECTS

5.1 Study subjects

Aplastic anemia (AA) subjects with thrombocytopenia refractory to immunosuppressive agents.

5.2 Inclusion criteria

Subjects may be included in the study if they meet all of the following criteria:

1) Patients who have provided written informed consent of their free will to participate in this clinical study. Written informed consent must be obtained prior to performing any study-related procedure
2) The subject is able and willing to comply with study procedures and follow-up as described in the protocol and ICF
3) Males and female subjects ≥ 19 years of age at the time of obtaining informed consent
4) Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of ≤ 2 at the time of screening
5) Diagnosis of AA, confirmed by bone marrow and cytogenetic studies
6) Patient who is refractory to immunosuppressive therapy (IST)
7) Prior treatment with at least one course of horse or rabbit anti-thymocyte globulin (ATG) with cyclosporine
8) Thrombocytopenia defined as platelet ≤ $30x10^9$/L
9) Fulfilling all of the following criteria in the screening examination
    - T-Bilirubin ≤ 1.5 times the upper limit of the laboratory normal range
    - ALT and AST ≤ 3 times the upper limit of the laboratory normal range
    - Creatinine ≤ 2.0 mg/dL

5.3 Exclusion criteria

Subjects must be excluded from participating in this study if they meet any of the following criteria:

1) Concurrent active infection not adequately responding to appropriate therapy
2) Human immunodeficiency virus positivity
3) Bone marrow reticulin grade of > 1 (Appendix 1)
4) Previous or concurrent active malignancies other than localized tumors diagnosed more than one year previously and treated surgically with curative intent (basal cell carcinoma or surgically resected in situ carcinoma of the cervix with apparent success ≥ 12 months prior to enrollment, as well as other cancers which have not been treated or have remained disease-free for at least 3 years before enrollment are eligible)
5) Clinically significant cardiac disease (class III or IV of the New York Heart Association (NYHA) classification; unstable angina pectoris, myocardial infarction within 6 months or is post angioplasty or stenting within 6 months; uncontrolled hypertension, clinically significant cardiac arrhythmia)
6) Arterial or venous thrombosis within the last 1 year before enrollment

7) Other cause of thrombocytopenia (for instance MDS, ITP, liver cirrhosis)
8) Subjects with AML or CMML
9) AA with hemolytic predominant PNH (hemolytic predominant is defined as LDH > 1.5 times the upper limit of the laboratory normal range)
10) Uncontrolled diabetes
11) Receiving other investigational agents within 16 weeks before starting the study treatment
12) Receiving any agent used to treat AA, including ATG or ATG+cyclosporine within 6 months before starting study treatment and/or cyclosporine or anabolic hormone within 6 weeks before starting the study treatment
13) History of PEG-rHuMGDF, recombinant human thrombopoietin, AMG531, and other TPO-receptor agonist
14) Who plans to conduct hematopoietic stem cell transplantation within 1 year
15) Known hypersensitivity to any recombinant *E. coli* derived product
16) Female subjects who are nursing or pregnant or are unwilling to take oral contraceptives or refrain from pregnancy if of childbearing potential
17) Subjects who are considered to be ineligible for the study by the investigator for reasons other than the above

5.4 Criteria for entering long-term treatment period

1) Subjects with platelet responses confirmed during 8 weeks prior to Week 53 (Week 46-Week 53)
2) Subjects who do not have any significant changes in medical condition during the initial evaluation period and extension period (Week 1-Week 52) including bone marrow stem cell disorders or new active malignancies

6 DOSING SCHEDULE AND CONCOMITANT THERAPY

6.1 Dose, dosing schedule, and treatment duration

There must be at least 3 days between the doses of AMG531 in each subject.

6.1.1 Initial-dose evaluation period (Week 1 to Week 8)

AMG531 will be administered at a dose of 1, 3, 6, or 10 µg/kg SC QW for 8 weeks. Dose adjustment (either escalation or reduction) will not be allowed during the initial dose evaluation period except for the cases defined in the 6.1.4 Criteria for discontinuing and resuming study treatment.

6.1.2 Extension period (Week 9 to Week 52)

Initial dose of AMG531 for the extension period will be decided based on the efficacy and safety data observed during the initial dose evaluation period. If a subject does not show a platelet response at Week 9, the dose will be increased by one level according to Table 6.1.2-1 AMG531 dose adjustment (extension period) table. If no platelet measurement is available due to the platelet transfusion, then that week's platelet response is considered as having no response.

6.1.2.1 Dose escalation

Dose escalation will be allowed during the extension period. If a subject does not show a platelet response after 4-week treatment with AMG531 at the previously escalated dose, the dose may be further increased by one level according to Table 6.1.2-1 at the discretion of the investigator, with the highest dose being 20 µg/kg. The necessity and timing of dose escalation after 4 week administration at a previously escalated dose will be decided by investigator after thorough consideration of the relevant safety and efficacy data for each subject.

6.1.2.2 Dose adjustment

If a subject shows a platelet response, the dose may be adjusted as appropriate to maintain the platelet response at the discretion of the investigator referring to the relevant efficacy and safety data of the each subject. For each dose adjustment, dose may be increased or decreased only by one level at a time according to the Table 6.1.2-1, with the highest dose being 20 µg/kg.

Table 6.1.2-1 AMG531 Dose adjustment table (extension period)

AMG531 Dose
1 µg/kg
3 µg/kg
6 µg/kg
10 µg/kg
13 µg/kg
16 µg/kg
20 µg/kg

6.1.3 Long-term treatment period (Week 53 to Week156)

6.1.3.1 Initial Dose

AMG531 will be administered SC QW at the same dose received as the last dose in the extension period. If dose adjustment is deemed to be necessary at Week 53 by investigator,

the dose may be adjusted according to the Table 6.1.3-1 Dose adjustment (long-term treatment period) table.

6.1.3.2 Dose adjustment

The dose may be adjusted as appropriate to maintain the platelet response at the discretion of the investigator. For each dose adjustment, dose may be increased or decreased only by one level at a time according to the Table 6.1.3-1, with the highest dose being 20 µg/kg and the lowest dose being 3 µg/kg.

Table 6.1.3-1 AMG531 Dose adjustment (long-term treatment period)

AMG531 Dose
3 µg/kg
6 µg/kg
10 µg/kg
13 µg/kg
16 µg/kg
20 µg/kg

6.1.3.3 Tapering and Discontinuation

If tri-lineage is maintained within normal level for 8-consecutive weeks with the same dose without transfusion, the dose will be decreased by one level at every 4 weeks. If tri-lineage is maintained within normal level for 4 consecutive weeks with 3 µg/kg without transfusion, AMG531 will be discontinued.

Normal level is defined as platelet counts $>50\times10^9$/L and hemoglobin concentration >10.0 g/dL and neutrophil counts $>1.0\times10^9$/L.

While tapering, if platelet counts drop to less than 30×10^9/L, hemoglobin to less than 9.0 g/dL, or neutrophil counts to less than 0.5×10^9/L, the tapering has to be stopped and dose will be adjusted following section 6.1.3.2. If the study drug were discontinued, it will be resumed at a dose of 3 µg/kg and further adjusted in accordance with section 6.1.3.2. Tapering may be tried again at the discretion of investigator.

While tapering, if patient does not meet the criteria of further tapering but maintains steady stable response, the dose will be kept stable. During tapering, dose reduction should follow section 6.1.3.3, not 6.1.3.2. While discontinuation, if patient maintains the steady stable response, dosing will not be resumed

6.1.4 Criteria for discontinuing and resuming study treatment

If the platelet has exceeded $400x10^9$/L during the treatment period, study treatment will be temporarily discontinued. Once the platelet count falls to $< 200x10^9$/L, administration of AMG531 will resume at a reduced dose by one level according to the protocol. Once the platelet count falls to $\leq 50x10^9$/L during the treatment with reduced dose by one level, dosing will be resumed at the temporarily discontinued dose.

If the platelet has exceeded $200x10^9$/L during the treatment period, the dose of AMG531 will be reduced to the next lower dose tested. If the temporarily discontinued dose is 1 µg/kg, treatment will be resumed at the dose of 1 µg/kg.

Other than the reasons above, investigator can reduce the dose at any time during the study if safety concerns arise.

6.2 Concomitant medications and therapies

6.2.1 Concomitant medications and therapies

Throughout the study period, investigator may prescribe any concomitant medications or therapies deemed necessary to provide adequate supportive care except for those listed in section 6.2.2. Rescue medication is defined as any medication that is administered to raise platelet counts, hemoglobin concentration or neutrophil counts. Rescue medication should only be administered when subjects is at immediate risk except for the case of transfusion. Platelet and RBC transfusions will be allowed during the study period as clinically indicated. Platelet counts, hemoglobin concentration and neutrophil counts determined after administration of rescue medication suspected to affect its level will not be used for the efficacy assessment. For the platelet transfusion, only single donor platelet (SDP) transfusion will be allowed during the study period.
Iron chelator will be allowed during the study period as clinically indicated.

6.2.2 Prohibited medications and therapies

While on study treatment, subjects are not permitted to receive any additional experimental medication or any therapy known or suspected to affect platelet production and AA from the time of enrollment throughout the study period. Examples of prohibited medications or therapies are follows;

1) Any investigational agents other than AMG531
2) TPO agonist other than AMG531

3) Other drugs to treat AA or symptoms associated with AA (e.g., immunosuppressive agents, cyclosporine, growth factors [For the case of G-CSF, its administration is only permitted as a rescue medication to treat infection, and will be prohibited for the purpose of treating AA])
4) Any medication known or suspected to affect platelet production
5) Hematopoietic stem cell transplantation

6.2.3 Recording concomitant medication and therapy in electronic Case Report Form (eCRF)

All concomitant medication and therapy that a subject received during the period after enrollment through to the end of the study will be recorded on electronic case report form (eCRF) by the investigator with the following information for each concomitant medication and therapy: name of drug, route of administration, duration of treatment and justification for the administration. Agents not intended for medical treatment such as rehydration including saline solution, dissolving solution, or contrast medium for imaging diagnostics are not required to be recorded.

Platelet transfusions given between the period within 56 days (Day -55) prior to the first administration of AMG531 (Day 1) and RBC transfusion given between the period of within 26 weeks (Day -181) prior to the first administration of AMG531 (Day 1) through to the end of study will be recorded in eCRF, including date of each transfusion, volume of transfusion (unit and mL), platelet count or hemoglobin concentration before each transfusion, and reason for each transfusion.

7 ENROLLMENT OF SUBJECTS

Before obtaining written informed consent from a subject, the investigator will examine the characteristics of each subject, as well as results of evaluations performed so far to select subjects who are expected to fulfill all of the inclusion criteria and not to meet any of the exclusion criteria.

The details of the study will be sufficiently explained by the investigator to the selected subjects, and those who agree to participate in the study will provide an informed consent. All subjects who have submitted an informed consent will be identified by subject identification code (SID) assigned by the investigative site and registered to interactive web response system (IWRS). The numbering conventions of SID are as shown below. SID assigned to each subject after obtaining the informed consent will be consistently used till the end of the study.

SID: 531-XX-YY

XX: Investigative site number (refer to the Study Protocol Supplement)

YY: Serial number of subjects given in chronological order of providing informed consent in each investigative site.

Example: SID of the first subject who provided informed consent in ## Hospital (Investigative site number, 01) will be 531-01-01.

The investigator will start treatment of each subject within 7 days after enrollment at an assigned dose.

8 OBSERVATIONS/ASSESSMENTS/EXAMINATIONS AND SCHEDULE

8.1 Schedule

The study schedule is shown in Table 8.1-1.

Table 8.1-1 Study schedule

〔Written informed consent to Week 8〕

Week	Screening Examination	1	2	3	4	5	6	7	8
Informed Consent	X								
Subject Background	X								
AMG531 Administration		X	X	X	X	X	X	X	X
Bone Marrow Examination	X								
Pregnancy Test	X								
ECOG PS	X								
Vital Signs	X	X	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X	X	X
Serum Chemistry	X	X	X	X	X	X	X	X	X
Blood Iron-Related Parameters[1)]	X	X				X			
Blood Coagulation and Fibrinolysis[2)]	X	X				X			
Folic Acid, Vitamin B_{12}	X								
Viral serologies for HIV, hepatitis B and C	X								
12-Lead ECG	X								
Flow cytometry for GPI-cells	X								
Serum AMG531 Concentration[3)]		X			X				X
Serum TPO Concentration		X							
Antibodies for AMG531 and TPO		X							
Cytokine assay		X							
GIMEMA bleeding scale		X							
Adverse Events		←	—	—	—	—	—	—	→
Concomitant Medications[4)]		←	—	—	—	—	—	—	→
PLT or RBC Transfusion	←	—	—	—	—	—	—	—	→

Week	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
AMG531 Administration	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum Chemistry	X				X				X				X			
Blood Iron-Related Parameters[1)]	X				X				X				X			
Blood Coagulation and Fibrinolysis[2)]	X				X				X				X			
Serum TPO Concentration	X															
Antibodies for AMG531 and TPO	X															
Cytokine assay	X															
GIMEMA bleeding scale	X															
Adverse Events	←	—	—	—	—	—	—	—	—	—	—	—	—	—	—	→
Concomitant Medications	←	—	—	—	—	—	—	—	—	—	—	—	—	—	—	→
PLT or RBC Transfusion	←	—	—	—	—	—	—	—	—	—	—	—	—	—	—	→

〔Week 9 to Week 52 (or withdrawal)〕

Week	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
AMG531 Administration	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Bone Marrow Examination	X[5)]															
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum Chemistry	X				X				X				X			
Blood Iron-Related Parameters[1)]	X				X				X				X			
Blood Coagulation and Fibrinolysis[2)]	X				X				X				X			
Antibodies for AMG531 and TPO	X															
Cytokine assay	X															
GIMEMA bleeding scale	X															
Adverse Events	←	—	—	—	—	—	—	—	—	—	—	—	—	—	—	→
Concomitant Medications	←	—	—	—	—	—	—	—	—	—	—	—	—	—	—	→
PLT or RBC Transfusion	←	—	—	—	—	—	—	—	—	—	—	—	—	—	—	→

Week	41	42	43	44	45	46	47	48	49	50	51	52
AMG531 Administration	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X	X	X	X	X	X
Serum Chemistry	X				X				X			
Blood Iron-Related Parameters[1)]	X				X				X			
Blood Coagulation and Fibrinolysis[2)]	X				X				X			
Antibodies for AMG531 and TPO	X											
Adverse Events	←	—	—	—	—	—	—	—	—	—	—	→
Concomitant Medications	←	—	—	—	—	—	—	—	—	—	—	→
PLT or RBC Transfusion	←	—	—	—	—	—	—	—	—	—	—	→

〔Week 53 to End of Study (or withdrawal)〕

Week	53 69 85 101 117 133 149	54 70 86 102 118 134 150	55 71 87 103 119 135 151	56 72 88 104 120 136 152	57 73 89 105 121 137 153	58 74 90 106 122 138 154	59 75 91 107 123 139 155	60 76 92 108 124 140 156	61 77 93 109 125 141	62 78 94 110 126 142	63 79 95 111 127 143	64 80 96 112 128 144	65 81 97 113 129 145	66 82 98 114 130 146	67 83 99 115 131 147	68 84 100 116 132 148	End of Treatment[8]	End of Study[9]
AMG531 Administration[12]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Bone Marrow Examination	Before dosing of AMG531 at W53, W77, W105, W129[5]																X[6]	
Vital Signs	X	X[11]	X	X[11]	X	X[11]	X	X[11]	X	X[11]	X	X[11]	X	X[11]	X	X[11]	X	X
Hematology	X	X[11]	X	X[11]	X	X[11]	X	X[11]	X	X[11]	X	X[11]	X	X[11]	X	X[11]	X	X
Serum Chemistry	X				X				X				X				X	X
Blood Iron-Related Parameters[1]	X				X				X				X				X	X
Blood Coagulation and Fibrinolysis[2]	X				X				X				X				X	X
12-Lead ECG	X[13]																X	
Serum AMG531 concentration																	X[7]	
Serum TPO Concentration	Before dosing AMG531 at W53, W105																X	
Antibodies for AMG531 and TPO	Before dosing AMG531 at W57, W77, W105, W129																	X
Cytokine assay	Before dosing AMG531 at W53 only																X[10]	
GIMEMA bleeding scale	Before dosing AMG531 at W53, W77, W105, W129																X	
Adverse Events	←																	→
Concomitant Medications	←																	→
PLT or RBC Transfusion	←																	→

1) Fe, TIBC, UIBC, TSAT and ferritin will be measured for the screening lab but starting from W1 to End of study, only ferritin level will be measured.

2) PT-INR, APTT and D-dimer will be measured for the screening lab but starting from W1 to End of study, only D-dimer will be measured.

3) Restricted to the patients assigned to AMG531 concentration test group. Refer to the Table 8.2.2-1 for detailed schedule and time windows for PK sample collections.

4) Information for the concomitant medication will be colleted after enrollment.

5) For the bone marrow examination, ± 2 weeks will be allowed

6) This bone marrow examination will be exempt for the patients withdrawn from the study within 11 weeks from the last bone marrow examination. Test time window of ± 2 weeks will be allowed.

7) Required only for premature termination at W8 or earlier.

8) One week after last administration of AMG531, or refer to the section 11.1.2 if subject is withdrawn from the study due to safety issues and cannot conduct the scheduled end of treatment visit.

9) Four weeks after last administration of AMG531, or refer to the section 11.1.2 if subject is withdrawn from the study due to safety issues and cannot conduct the scheduled end of study visit.

10) This cytokine assay will be required only for the patients withdrawn from the study before Week 53.

11) Subjects on discontinuation of AMG531 after achieving normal level for 8 consecutive weeks without transfusion (refer to the section 6.1.3.3) can skip even-numbered visit (i.e make bi-weekly visits).

12) For those who discontinued the AMG531 after achieving normal level for 8 consecutive weeks without transfusion (refer to the section 6.1.3.3), dosing will be skipped.

13) Required only at Week53 before dosing of AMG531

8.2 Observations/assessments/examinations and schedule

8.2.1 Screening examinations

A signed and dated IRB approved informed consent must be obtained before any study specific procedures are performed. Procedures that are part of routine care are not considered as study specific procedures.

The screening period begins on the date of subject signed the IRB approved informed consent and continues until the date of first administration of AMG531. The following screening examination will be conducted within 4 weeks prior to the first administration of AMG531 (Week -4 to Day 1). Retesting during this period may be performed as needed.

Subjects who fail screening will be allowed to be re-screened if a remediable cause for the original screen failure is found.

1) Baseline characteristics: date on which the subject is diagnosed with AA, severity of AA (Appendix 2), previous treatments for AA (duration and sort of treatment), baseline platelet count, platelet transfusion in the previous 8 weeks prior to the first administration of AMG531 (Day -55 to Day 1), RBC transfusion in the previous 26 weeks prior to the first administration of AMG531 (Day -181 to Day1), concomitant medications, medical history, current complications, date of birth, gender, weight, and height, baseline platelet count according to the protocol Master Ver1.1 (The mean of two lowest platelet counts measured in 8 weeks prior to enrollment. Platelet count that is obtained within 3 days after platelet transfusion will not be used)
2) Bone marrow biopsy and aspiration with cytogenetics (M/E ratio, celluarity of bone marrow, reticulin grade (reticulin stain/trichrome stain (Appendix 1)), iron stain, narrative pathology report, cytogenetic report and exploratory test described in section 3.3.4)
3) Pregnancy test (excluding male subjects and female subjects underwent oophorectomy or hysterectomy or those who are non-childbearing potential i.e., menstrual periods have been absent for at least 12 months)
4) ECOG PS

5) Vital signs (systolic blood pressure, diastolic blood pressure and pulse rate)
6) Hematology (WBC, RBC, Hb, Ht, MCV, MCH, MCHC, PLT, Ret and WBC with differential count)
7) Serum chemistry (TP, ALB, T-Bil, D-Bil, AST, ALT, ALP, LDH, γ-GTP, T-Cho, UA, BUN, Cr, Na, K, Ca, P and Cl)
8) Blood iron-related parameters (Fe, TIBC, UIBC, TSAT and ferritin)
9) Blood coagulation and fibrinolysis (PT-INR, APTT and D-dimer)
10) Folic acid and vitamin B_{12}
11) Viral serologies for HIV, hepatitis B and C
12) 12-lead ECG
13) Flow cytometry of the peripheral blood for GPI-cells

8.2.2 Treatment Period: Week 1 (day of initial administration of AMG531) to Week 8

The following observations and examinations during the period of Week 1 (day of initial treatment with AMG531) through to Week 8 will be conducted on the day of study treatment, as a general rule. In consideration of convenience for subjects and investigational sites, ± 3 days will be allowed except for the subjects assigned to the AMG531 concentration test group. Subjects on dose interruption will also undergo the same observations and examinations. Serum for the determination of AMG531 concentration can be collected at Week 1, Week 4 and Week 8 as described in Table 8.2.2-1 Schedule for PK sampling.

1) Vital signs (systolic blood pressure, diastolic blood pressure and pulse rate)

   Timing of measurement: Every week before dosing AMG531 in Week 1 to Week 8

2) Hematology (WBC, RBC, Hb, Ht, MCV, MCH, MCHC, PLT, Ret and WBC with differential count)

   Timing of measurement: Every week before dosing AMG531 in Week 1 to Week 8

3) Serum chemistry (TP, ALB, T-Bil, D-Bil, AST, ALT, ALP, LDH, γ-GTP, T-Cho, UA, BUN, Cr, Na, K, Ca, P and Cl)

   Timing of measurement: Every week before dosing AMG531 in Week 1 to Week 8

4) Blood iron-related parameter (ferritin)

   Timing of measurement: Before dosing AMG531 at Week 1 and Week 5

5) Blood coagulation (D-dimer)

   Timing of measurement: Before dosing AMG531 at Week 1 and Week 5

6) Serum AMG531 concentration

Timing of measurement: Before dosing and 4, 12, 24, 48, 72, 96, and 168 hours after dosing AMG531 at Week 1 and Week 8, and before dosing AMG531 at Week 4. Detailed time point with sampling time window is described in Table 8.2.2-1.

7) Serum TPO concentration

   Timing of measurement: Before dosing AMG531 at Week 1

8) Antibodies against AMG531 and TPO

   Timing of measurement: Before dosing AMG531 at Week 1 (Additional antibody test can be performed on subjects who show clinical findings suggested of possible antibody formation)

9) Cytokine assay

   Timing of measurement: Before dosing AMG531 at Week 1

10) GIMEMA bleeding scale (Appendix 3)

    Timing of measurement: Before dosing AMG531 at Week 1

Table 8.2.2-1 Schedule for PK sampling

Study Week	Study date	Time of Collection	
Week 1	Day 1	Before dosing of AMG531	within 2 hours
		After dosing of AMG531	4 hours ± 30 minutes
			12 hours ± 90 minutes
	Day 2		24 hours ± 3 hours
	Day 3		48 hours ± 3 hours
	Day 4		72 hours ± 3 hours
	Day 5		96 hours ± 3 hours
	Day 8[1)]		168 hours ± 3 hours
Week 4	Day 22	Before dosing of AMG531	within 2 hours
Week 8	Day 50	Before dosing of AMG531	within 2 hours
		After dosing of AMG531	4 hours ± 30 minutes
			12 hours ± 90 minutes
	Day 51		24 hours ± 3 hours
	Day 52		48 hours ± 3 hours
	Day 53		72 hours ± 3 hours
	Day 54		96 hours ± 3 hours
	Day 57[2)]		168 hours ± 3 hours

1) The examination at 168 hours after dosing AMG531 at Week 1 will be conducted before dosing AMG531 at Week 2

2) The examination at 168 hours after dosing AMG531 at Week 8 will be conducted before dosing AMG531 at Week 9

8.2.3 Treatment Period: Week 9 to Week 52

The following observations and examinations during Week 9 through to Week 52 will be conducted on the day of study treatment, as a general rule. In consideration of

convenience for subjects and investigational sites, ± 3 days will be allowed. Subjects on dose interruption will also undergo the same observations and examinations.

1) Vital signs (systolic blood pressure, diastolic blood pressure, and pulse rate)

   Timing of measurement: Every week before dosing AMG531 at Week 9 through to Week 52

2) Hematology (WBC, RBC, Hb, Ht, MCV, MCH, MCHC, PLT, Ret and WBC with differential count)

   Timing of measurement: Every week before dosing AMG531 at Week 9 through to Week 52

3) Serum chemistry (TP, ALB, T-Bil, D-Bil, AST, ALT, ALP, LDH, γ-GTP, T-Cho, UA, BUN, Cr, Na, K, Ca, P and Cl)

   Timing of measurement: Before dosing AMG531 at Week 9, 13, 17, 21, 25, 29, 33, 37, 41, 45 and 49

4) Blood iron-related parameter (ferritin)

   Timing of measurement: Before dosing AMG531 at Week 9, 13, 17, 21, 25, 29, 33, 37, 41, 45 and 49

5) Blood coagulation (D-dimer)

   Timing of measurement: Before dosing AMG531 at Week 9, 13, 17, 21, 25, 29, 33, 37, 41, 45 and 49

6) Bone marrow biopsy and aspiration with cytogenetics (M/E ratio, celluarity of bone marrow, reticulin grade (reticulin stain/trichrome stain (Appendix 1)), iron stain, narrative pathology report, cytogenetic report and exploratory test described in section 3.3.4).
   Timing of measurement: Before dosing AMG531 at Week 25 ± 2 weeks

7) Serum TPO concentration

   Timing of measurement: Before dosing AMG531 at Week 9

8) Antibodies against AMG531 and TPO

   Timing of measurement: Before dosing AMG531 at Week 9, Week 25 and Week 41 (Additional antibody test can be performed on subjects who show clinical findings suggested of possible antibody formation)

9) Cytokine assay

   Timing of measurement: Before dosing AMG531 at Week 9 and Week 25

10) GIMEMA bleeding scale (Appendix 3)

    Timing of measurement: Before dosing AMG531 at Week 9 and Week 25

8.2.4 Treatment Period: Week 53 to Week 156

The following observations and examinations during Week 53 through to Week 156 will be conducted on the day of study treatment, as a general rule. In consideration of

convenience for subjects and investigational sites, ± 3 days will be allowed. Subjects on dose interruption or tapering will also undergo the same observations and examinations. For those on dose discontinuation after achieving tri-lineage normal level for 8 consecutive weeks without transfusion according to section 6.1.3.3 will be visiting site in every 2 weeks.

1) Vital signs (systolic blood pressure, diastolic blood pressure, and pulse rate)
   Timing of measurement: Every week before dosing AMG531 at Week 53 through to Week 156 [For subjects on drug discontinuation: every 2 weeks before dosing AMG531 at Week 53 through to Week 156]
2) Hematology (WBC, RBC, Hb, Ht, MCV, MCH, MCHC, PLT, Ret and WBC with differential count)
   Timing of measurement: Every week before dosing AMG531 at Week 53 through to Week 156 [For subjects on drug discontinuation: every 2 weeks before dosing AMG531 at Week 53 through to Week 156]
3) Serum chemistry (TP, ALB, T-Bil, D-Bil, AST, ALT, ALP, LDH, γ-GTP, T-Cho, UA, BUN, Cr, Na, K, Ca, P and Cl)
   Timing of measurement: Every 4 weeks before dosing AMG531 at Week 53 through to Week 156
4) Blood iron-related parameter (ferritin)
   Timing of measurement: Every 4 weeks before dosing AMG531 at Week 53 through to Week 156
5) Blood coagulation (D-dimer)
   Timing of measurement: Every 4 weeks before dosing AMG531 at Week 53 through to Week 156
6) 12-lead ECG
   Timing of measurement: Required only at Week53 before doing of AMG531
7) Bone marrow biopsy and aspiration with cytogenetics (M/E ratio, celluarity of bone marrow, reticulin grade (reticulin stain/trichrome stain (Appendix 1)), iron stain, narrative pathology report, cytogenetic report and exploratory test described in section 3.3.4).
   Timing of measurement: Before dosing AMG531 at Week 53, Week 77, Week 105, Week 129. ± 2 weeks will be allowed.
8) Serum TPO concentration
   Timing of measurement: Before dosing AMG531 at Week 53, Week105
9) Antibodies against AMG531 and TPO
   Timing of measurement: Before dosing AMG531 at Week 57, Week 77, Week 105, Week 129 (Additional antibody test can be performed on subjects who show clinical findings suggested of possible antibody formation)
10) GIMEMA bleeding scale (Appendix 3)
   Timing of measurement: Before dosing AMG531 at Week 53, Week 77, Week 105, Week 129

8.2.5 End of treatment: one week after last administration of AMG531

All subjects who completed the study treatment will undergo the following observations, assessments and examinations one week after the last administration of AMG531. In consideration of convenience for subjects and investigational sites, ± 3 days will be allowed.

Subjects exposed to AMG531 but terminated the study treatment earlier than scheduled will undergo the same observations, assessments and examinations one week after their last administration of AMG531. In consideration of convenience for subjects and investigational sites, ± 3 days will be allowed.

1) Vital signs (systolic blood pressure, diastolic blood pressure, and pulse rate)
2) Hematology (WBC, RBC, Hb, Ht, MCV, MCH, MCHC, PLT, Ret and WBC with differential count)
3) Serum chemistry (TP, ALB, T-Bil, D-Bil, AST, ALT, ALP, LDH, γ-GTP, T-Cho, UA, BUN, Cr, Na, K, Ca, P and Cl)
4) Blood iron-related parameter (ferritin)
5) Blood coagulation (D-dimer)
6) Bone marrow biopsy and aspiration with cytogenetics (M/E ratio, celluarity of bone marrow, reticulin grade (reticulin stain/trichrome stain (Appendix 1)), iron stain, narrative pathology report, cytogenetic report and exploratory test described in section 3.3.4) (to be exempt for the patient withdrawn from the study within 11 weeks from the last bone marrow examination). Time window ± 2 weeks will be allowed.
7) Serum AMG531 concentration (only at withdrawal in Week 8 or earlier)
8) Serum TPO concentration
9) Cytokine assay (To be required only for the patients withdrawn from the study before Week 53)
10) GIMEMA bleeding scale (Appendix 3)
11) 12-Lead ECG

8.2.6 End of study: four weeks after last administration of AMG531

All subjects should complete an end of study visit four weeks after their last administration of AMG531. In consideration of convenience for subjects and investigational sites, ± 3 days will be allowed.

Subjects exposed to AMG531 but terminated the study treatment earlier than scheduled will undergo the same observations, assessments and examinations four weeks after their last administration of AMG531. In consideration of convenience for subjects and investigational sites, ± 3 days will be allowed.

1) Vital signs (systolic blood pressure, diastolic blood pressure, and pulse rate)
2) Hematology (WBC, RBC, Hb, Ht, MCV, MCH, MCHC, PLT, Ret and WBC with differential count)
3) Serum chemistry (TP, ALB, T-Bil, D-Bil, AST, ALT, ALP, LDH, γ-GTP, T-Cho, UA, BUN, Cr, Na, K, Ca, P and Cl)
4) Blood iron-related parameter (ferritin)
5) Blood coagulation (D-dimer)
6) Antibodies against AMG531 and TPO

8.2.7 Outcome surveillance for Survival, AML/MDS transformation, and cytogenetic abnormality

All subjects received at least one dose of AMG531 will be assessed for the following parameters. The results of the survey will be reported using the outcome surveillance form (refer to Attachment 1 of the Study Protocol Supplement.

1) Parameters
   - Survival (date of confirmation) or death (date and cause of death).
   - Presence or absence of cytogenetic abnormality (date of confirmation, cellularity of bone marrow, karyotype by cytogenetic report)
   - Presence or absence of fibrosis according to reticulin grade (reticulin stain/trichrome stain (Appendix 1))
   - Presence or absence of AML or MDS transformation (date of initial diagnosis in case of presence, or date of last confirmation in case of absence)
   - Presence or absence of Hematopoietic Stem Cell Transplantation (date of transplantation, or the last date of confirmation in case of absence)
2) Timing of assessment
   - Approximately 3 years after the initial administration of AMG531 and whenever required by the regulatory authority or investigators.

9 ADVERSE EVENTS

9.1 Definition of adverse events

An adverse event (AE) is herein defined as any untoward medical occurrence in subjects received AMG531. An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom or disease, regardless of causal relationship to AMG531. An adverse drug reaction (ADR) is defined as any AE of which causal relationship to AMG531 cannot be ruled out (any events assessed to be other than “unlikely” or “not related”).

Laboratory results (hematology, serum chemistry, blood iron-related parameters, blood coagulation and fibrinolysis) will be evaluated for deviations (abnormalities) from normal range of each investigative site. In the event of an abnormal value (abnormal change), clinically significance of the abnormal change in comparison with baseline will be assessed. In consideration of pharmacological effects of AMG531, an increase in platelet, hemoglobin, reticulocyte, and/or neutrophil will be treated as abnormal only in the cases where the investigator considers it to be medically important.

For signs, symptoms, and abnormal laboratory findings associated with a disease (diagnosed disease), the disease will be treated as an AE. If any atypical sign is observed in that disease, the sign will be treated as an individual AE.

Observation period of both non-serious and serious adverse events will be the period between the start of study treatment through to the end of study visit or 4 weeks after the last administration of AMG531, whichever is longer. However, any event reported as delayed toxicity or the like attributed the investigational product will be treated as an adverse event as well.

9.1.1 Definition of serious adverse events

A serious adverse event (SAE) is any adverse event that:

1) Results in death;
2) Is life-threatening;
3) Requires inpatient hospitalization or prolongation of existing hospitalization (excluding a hospitalization needed for medical examinations and a hospitalization planned before the start of the study);
4) Results in disability/incapacity;
5) Results in potential disability;
6) Results in other conditions as important as 1) to 5); or
7) Is a congenital anomaly/birth defect.

9.1.2 Definition of other significant adverse events

Other significant AEs are defined as any events other than those reported as SAEs that lead a subject to treatment interruption, dose reduction or withdrawal.

9.2 Safety assessment parameters

For safety assessment, the following parameters will be investigated.

The investigator will follow subjects with AEs until the event has recovered to the pretreatment level or archived the condition which is not clinically important, excluding the cases where the investigator considers that the safety of the relevant subject is sufficiently assured and further follow-up is not necessary. Any action taken for the AE during the follow-up will be recorded on the eCRF.

1) Name of AE
2) Date of onset
3) Severity

Severity will be graded using the 5-point scale, Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. AEs to which the CTCAE severity scale is not applicable will be graded as described below:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal local or noninvasive intervention indicated; limiting age-appropriate instrumental active daily living (preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc).
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care active daily living (bathing, dressing and undressing, self feeding, using the toilet, taking medications, and not bedridden).
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE

4) Seriousness
    - Serious: Events defined in Section 9.1.1.
    - Non-serious: Events other than those defined in Section 9.1.1.
5) Actions taken for the study treatment
    - None/not applicable
    - Dose reduced
    - Dose interrupted
    - Discontinued
6) Other actions taken
    - None
    - Other medication prescribed or concomitant medication changed, etc.
7) Outcome
    - Resolved/recovered
    - Resolving/recovering

- Not resolved/not recovered
- Resolved/recovered with squeal
- Death
- Unknown

8) Date of outcome assessment
9) Causal relationship to investigational product

   Causal relationship to investigational product will be determined using the following 5-point scale.

   - Certain
   - Probable
   - Possible
   - Unlikely
   - Not related

9.3 Actions to be taken on occurrence of an adverse event and follow-up

9.3.1 Actions for Subjects

If an AE occurs, the investigator will take appropriate actions as needed, including providing proper medical care and discontinuing study treatment in order to ensure the subject's safety.

9.3.2 Notification to the concerned parties (reporting to relevant personnel)

9.3.2.1 Serious adverse event

1) If a SAE occurs, regardless of the causal relationship with AMG531, the investigator will immediately (within 24 hours of the investigator becoming aware of the event) notify the sponsor or the designee in person or by phone, e-mail, or fax (using the SAE Report or a form prescribed by the investigative site) and will promptly (within 7 days of the investigator becoming aware of the event) submit a detailed written report to the sponsor or the designee and the IRB. When reporting to the IRB, unexpected serious adverse reactions should be identified.
2) The investigator is obligated to pursue and provide additional information upon request from the sponsor or the designee, the directors of investigative sites and the IRB.
3) The director of the investigative site will discuss with the IRB whether to continue the study at their site, if applicable.

4) In the case of serious and unexpected ADRs that are fatal or life-threatening, the sponsor or the designee should expedite the report to all concerned investigators, to the IRBs where required, and to the regulatory authorities within 7 days after first knowledge by the sponsor. Serious, unexpected reactions (ADRs) that are not fatal or life-threatening must be filed within 15 days after first knowledge by the sponsor.

9.3.2.2 Non-serious adverse events

If a noteworthy but non-serious AE occurs, the investigator will promptly provide the sponsor with a description of the event and the action taken. Other adverse events will be recorded in the eCRF.

9.3.3 Follow-up of adverse events

The investigator will follow subjects with AEs until the event has recovered to the pretreatment level or archived the condition which is not clinically important, excluding the cases where the investigator considers that the safety of the relevant subject is sufficiently assured and further follow-up is not necessary. Any action taken for the AEs during the follow-up will be recorded in the eCRF.

10 MANAGEMENT OF SUBJECTS; MEASURE FOR PATIENTS' SAFETY PROTECTION

10.1 Notification to other departments/hospitals

The investigator will check with the subject if he/she is scheduled to receive medical care or medications at any other department/hospital. If this is the case, the investigator will notify the relevant physician that the subject will participate in the clinical study. The investigator will identify the name of any medication that the subject has received other than those prescribed by the investigator as well as how it has been used. If the subject received platelet and/or RBC transfusion at any other department/hospital, investigations should be made in the same manner.

If the subject is newly receives medical care or medication at any other department/hospital during the study, the investigator will take actions same as above.

10.2 Contraception

Women of childbearing potential will be instructed to use one or more reliable methods of contraception (including condoms) throughout the study.

If the subject becomes pregnant or wants to have children during the study, the subject will be immediately withdrawn from the study.

10.3 Others

The eligibility of the subject to participate in the study will be strictly assessed through the screening test.

In addition, the study will be conducted in compliance with the study protocol, and the occurrence and severity of AEs and ADRs will be monitored throughout the study period and the appropriate actions will be taken when needed for the protection of subjects.

11 STOPPING RULES AND PROCEDURES

11.1 Subject withdrawal

11.1.1 Criteria for subject withdrawal

Any of the following circumstances will result in the subject being withdrawn from the study:

1) The subject is found to be ineligible for participation in this study due to violations in the inclusion or exclusion criteria specified in the study protocol;
2) The subject decides to discontinue his/her participation in the study;
3) The subject becomes unable to undergo necessary observations or examinations;
4) The subject who does not achieve a platelet response after 8-week treatment with AMG531 20 μg/kg QW;
5) The investigator considers that the subject should be withdrawn from the study due to an adverse event (including progression of the primary disease);
6) The subject received any of the prohibited concomitant medications or treatments;
7) The subject becomes pregnant or wants to have children during the study;
8) The investigator assesses that the subject needs to be withdrawn from the study for any reason not specified above.
9) The subject who does not meet the entry criteria for long-term treatment period

11.1.2 Procedure for subject withdrawal

If a subject is withdrawn from the study because of safety issues including occurrence of an adverse event, the investigator will provide appropriate treatment for the subject. For each subject withdrawn from the study, the investigator will check up the safety and

conduct the end of treatment and end of study procedures described in section 8.2.5 and 8.2.6 at withdrawal and follow him/her up as necessary until further monitoring is considered to be not required. If subject is withdrawn from the study due to safety issues and cannot conduct the scheduled end of treatment and end of study procedures, the end of treatment and end of study procedures described in section 8.2.5 and 8.2.6 will be conducted as soon as the study termination is decided. It is recommended that subjects withdrawn consent also return to the physician's office for the end of treatment and end of study examination for follow up.

Date and the reasons of study withdrawal, any medications given for the treatment during the follow up period, etc. will be recorded in the eCRF.

11.2 Premature termination or suspension of the study at a specific investigative site

If the investigator prematurely terminates or suspends the study at his/her site due to concerns over the safety of investigational product or for any other reason, the investigator will promptly notify the sponsor and IRB in writing, with a written detailed explanation. Also, if the investigative site's IRB says that the study should not be continued, the investigator will promptly notify the sponsor in writing, with a written detailed explanation on the study termination or suspension. The investigative site has major or continuous violations of GCP, the protocol or the clinical study agreements, the study will be prematurely terminated at the site. In such event, appropriate actions will be taken in the same manner to the above.

11.3 Premature termination or suspension of the entire study

When the entire study needs to be prematurely terminated or suspended, the sponsor will promptly inform all investigators, IRB, and the regulatory agency with a detailed explanation of the reason. When the study is prematurely terminated or suspended, the investigator will promptly brief subjects and take necessary measures including providing appropriate medical care.

12 STATISTICAL ANALYSIS

12.1 Statistical methods

Generally, categorical variables will be summarized by the number of subjects and the percentage of subjects in each category to the total number of subjects, and continuous variables will be summarized by descriptive statistics (number of subjects, mean, standard deviation, median, minimum, and maximum). Coefficient of variation and geometric mean will be also presented to summarize pharmacokinetic parameters.

Data will be cut off, collected and analyzed when all subjects complete the observations at week 17.

12.1.1 Efficacy

Platelet count measured within 7 days after platelet transfusion will not be subjected to the efficacy assessment. Likewise, hemoglobin concentrations determined within 28 days after RBC transfusion will not be subjected to the efficacy assessment. Neutrophil counts determined within 7 days of G-CSF as a rescue medication will not be used for the efficacy assessment.

Platelet count, hemoglobin concentrations and neutrophil counts determined in occasions other than in the scheduled visit in this study, including ordinary medical examinations and follow-up, will not be used for efficacy assessment.

12.1.1.1 Primary endpoint

The primary endpoints will be evaluated based on the Per Protocol Set (PPS). The proportion of subjects achieving a platelet response at Week 9, and two-sided 95% confidence interval will be calculated. Platelet response is defined as 1) achieving absolute platelet increase of $\geq 20x10^9$/L above baseline or 2) increase to $\geq 10x10^9$/L and by at least 100% from baseline.

Robustness of the results will be evaluated by the analysis calculated in the same manner based on the full analysis set (FAS).

12.1.1.2 Secondary endpoint

The secondary endpoint will be evaluated based on the PPS. The proportion of subjects with a platelet response in any time during the initial dose evaluation period, Week1 through Week 12, Week 1 through Week 16, Week 1 through Week 24, and Week 1 through Week 52 or the proportion of subjects achieving platelet transfusion independency during the initial dose evaluation period, Week1 through Week 12, Week 1 through Week 16, Week 1 through Week 24, Week 1 through Week 52, Week 1 through Week 104, and Week1 through Week 156 will be calculated in the same manner as the primary variables. Platelet transfusion independence is defined as achieving transfusion free period of at least 8 consecutive weeks.

The proportion of subjects with erythroid and/or neutrophil response during the initial dose evaluation period as well as in Week1 through Week 12, Week 1 through Week 16, Week1 through Week 24, Week 1 through Week 52, Week 1 through Week 104, and in

Week1 through Week 156 will be calculated in the same manner as the primary variables. An erythroid response is defined as achieving an increase in hemoglobin concentration of $\geq$ 1.5 g/dL above baseline without transfusion or reduction in the transfusion unit by at least 4 units for 8 consecutive weeks compared with the pretreatment transfusion requirement in the previous 8 weeks prior to the first administration of AMG531 (Day -55 to Day 1). A neutrophil response is defined in those with ANC of $< 0.5 \times 10^9$/L as a 100% increase over the baseline, or an increase in ANC of $> 0.5 \times 10^9$/L in subjects with a pretreatment ANC of $< 1.0 \times 10^9$/L.

Time to platelet response and duration of platelet response will be summarized.

The change in platelet counts, hemoglobin concentrations, and neutrophil counts from baseline will be summarized at each scheduled visit. For the transfusion, only the platelet transfusion given due to platelet count of $< 10 \times 10^9$/L (prophylactic transfusion) or due to bleeding (therapeutic transfusion) and RBC transfusions of which hemoglobin concentration is $\leq$ 9.0 g/dL or due to symptomatic anemia will be included in the response assessment.

The changes in bone marrow celluarity and reticulin grade will be summarized by each subject based on the test reports. The changes in the GIMEMA bleeding scale will be summarized.

Tri-lineage response is defined in those achieving platelet response, erythroid response, and neutrophil response all together. The proportion of subjects with tri-lineage response will be calculated in the same manner as the primary variables. Time to tri-lineage response will be summarized.

The proportion of subjects who achieved normal level for 8 consecutive weeks, who started tapering, and who discontinued study drug will be calculated. Time to achieving normal level for 8 consecutive weeks (the initial day of the period), to starting tapering, to discontinuing study drug as a result of tapering will be summarized.

Longest duration of drug discontinuation in subjects while maintaining stable response will be summarized.

Robustness of the results will be evaluated by the analysis calculated in the same manner based on the FAS.

12.1.2 Pharmacokinetics

1) Serum AMG531 concentration

Serum AMG531 concentration will be summarized by descriptive statistics for each dose group at each sampling point. Time course of the serum concentrations of AMG531 will be presented in a chart.

2) Pharmacokinetic parameters

Pharmacokinetic parameters (including T_{max}, C_{max}, AUC_{0-t}) will be calculated for each subject and summarized by descriptive statistics for each dose group. Dose proportionality will be also assessed.

12.1.3 Safety

All AEs will be tabulated by MedDRA Preferred Terms (PTs) and System Organ Classes (SOCs) and number as well as percentage of subjects with each AE will be calculated by dose group. ADRs will be summarized in the same manner. All AEs will be graded with CTCAE ver.4.0 and number and percentage of subjects for each AE will be calculated.

All AEs occurred during the initial dose evaluation period will be separately summarized and analyzed as above.

Laboratory tests and vital signs will be summarized by descriptive statistics for all examination points of each dose group.

A listing of subjects with positive antibody against AMG531, TPO and TMPwill be summarized by antibody expression.

12.1.4 Additional analyses

Additional exploratory analyses of the data will be performed as deemed to be appropriate.

12.2 Level of significance

Level of significance is not specified, since no statistical assumptions are provided in this study.

12.3 Stopping rules for the study

No stopping rules based on statistical evidence are specified.

12.4 Handling of missing, unused, and abnormal data

Any missing data on platelet, hemoglobin, and neutrophil for evaluating efficacy response will be handled as a missing value and will not be imputed with an alternative value using a statistical approach.

If data from a particular subject needs to be examined how to handle them because of an event unexpected at the start of the study, how to treat such data will be decided before database lock.

12.5 Development of the statistical analysis plan and procedure for reporting deviations from the original statistical analysis plan

The detailed statistical analysis plan including the analyses described in this section will be finalized before database lock. Any major change to the statistical analysis plan will be described in the clinical study report.

12.6 Analysis Subsets

The analysis sets are defined below. For efficacy analysis, PPS and FAS will be used, with PPS as the primary analysis set.

Whether or not to include each subject in a particular set will be determined before database lock.

12.6.1 Full Analysis Set (FAS)

Efficacy will be assessed in the subjects of FAS who meet all of the following criteria:

- Subjects received at least one dose of AMG531; and
- Subjects whose platelet count is measured before and at least one point after dosing AMG531.

12.6.2 Per Protocol Set (PPS)

Efficacy will be assessed in the population of PPS comprised of subjects of FAS who meet all the following criteria. PPS is the primary efficacy analysis set.

- Subjects who meet all of the inclusion criteria and none of the exclusion criteria;
- Subjects who have received ≥ 6 times of the specified dose (dose interruption according to the dose discontinuation criteria (section 6.1.3) will be considered as

being dosed but dose interruption due to SAE will not be considered as being dosed) in the initial dose evaluation period; and

- Subjects with no major violations of the study protocol in the initial dose evaluation period.

12.6.3 Pharmacokinetic analysis set

Pharmacokinetics will be evaluated in the subjects whose serum AMG531 concentrations are measured and who meet all of the following criteria:

- Subjects received at least one dose of AMG531; and
- Subjects whose at least one pharmacokinetic parameter is calculable.

12.6.4 Safety analysis set

Safety will be assessed in the subjects of safety analysis set who meet the following criterion:

- Subjects received at least one dose of AMG531.

13 ETHICS

13.1 Regulatory considerations

The study will be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the ICH guidelines on GCP, any applicable laws and requirements, and any conditions required by a regulatory authority and/or IRB that approves this study to be conducted in its territory. Good clinical practice is defined as a standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical studies in a way that provides assurance that the data and reported results are credible and accurate, and that the rights, safety, and well-being of study subjects are protected.

Per GCP, the protocol will be reviewed and approved by the IRB of each participating center prior to study initiation. Serious adverse events regardless of causality will be reported to the sponsor, and the investigator will keep the IRB informed as to the progress of the study.

The investigator will explain the nature of the study and will inform the subject that participation is voluntary and that the subject can withdraw or be withdrawn from the study at any time. Written informed consent will be obtained from each subject prior to the screening procedures to determine if study eligibility criteria are met. A copy of the

signed consent form will be given to every subject, and the original will be maintained with the subject's records.

13.2 Institutional Review Board

A list of IRB members or a Statement of GCP Compliance should be obtained by the investigator and provided to the sponsor.

Any documents that the IRB may need to fulfill its responsibilities, such as protocol amendments, and information concerning subject recruitment, payment, or compensation procedures, or information from the sponsor will be submitted to the IRB. The IRB's written unconditional approval of the study protocol, the informed consent form(s), and any other written materials to be provided to subjects will be in the possession of the investigator and the sponsor before the study is initiated. The IRB's unconditional approval statement will be transmitted by the investigator to the sponsor prior to shipment of investigational product supplies to the investigative site. This approval must refer to the study by exact protocol title and number, and should identify the documents reviewed and the date of review.

Protocol modifications or changes may not be initiated without prior written IRB approval except when necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB and written verification that the modification was submitted should be obtained.

The IRB must be informed by the investigator of informed consent form changes or revisions of other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study; new information that may affect adversely the safety of the subjects or the conduct of the study; an annual update and/or request for reapproval; and when the study has been completed.

13.3 Informed Consent

Freely given informed consent will be obtained and documented for all subjects under this protocol in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the ICH guidelines on GCP, any applicable laws and requirements, and any conditions required by a Regulatory Authority and/or IRB.

Information should be given in both oral and written form, and subjects must be given ample opportunity to inquire about details of the study.

The consent form(s) generated by the investigator must be approved by the IRB and be acceptable to the sponsor. Consent forms must be written so as to be understood by the prospective subject. Informed consent will be documented by the use of a written consent form(s) approved by the IRB and signed and dated by the subject, and by the person who conducted the informed consent discussion. The signature confirms the consent is based on information that has been understood. Each subject's signed informed consent form(s) must be kept on file by the investigator for possible inspection by the sponsor or its designated monitors, auditors, or regulatory agency representatives. The subject should receive a copy of the signed and dated written informed consent form(s) and any other written information provided to the subject, and should receive copies of any signed and dated consent form updates and any amendments to the written information provided to subjects.

14 FINANCING AND INSURANCE

Financing and insurance are detailed in the individual site contracts.

15 PROTOCOL DEVIATIONS

The investigator should notify the IRB and the sponsor of deviations from the protocol in accordance with local regulation/procedures.

The investigator should conduct the study in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority, and which was given approval/favorable opinion by the IRB.

A deviation to any protocol procedure or waiver to any stated criteria will not be allowed in this study except where necessary to eliminate immediate hazard(s) to the subject. The sponsor must be notified of all intended or unintended deviations to the protocol (e.g., inclusion/exclusion criteria, missed study visits) on an expedited basis.

The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

Any data recorded in eCRF will be collected and included in the database. If a subject was ineligible or received the incorrect dose or investigational treatment, and had at least one administration of investigational product, data should be collected for safety purposes.

16 DATA MANAGEMENT

Appropriately validated standard computer systems will be used by the sponsor involved in this study.

The Electronic Data Capture (EDC) system is to provide investigative sites with the functions for entering data directly in eCRFs, for querying inconsistent data, for answering queries on entered information from the sponsor, and for electronic signature. The entered information will be coded and sent to the EDC server via the Internet.

The investigator will sign the eCRF via the EDC system's electronic signature. These signatures will indicate that the investigator inspected or reviewed the data on the eCRF, the data queries, and the site notifications, and agrees with the content.

Instructions will be provided for the completion of the eCRF and any corrections made will be automatically documented via the EDC software's "audit trail".

17 DIRECT ACCESS TO SOURCE DOCUMENTS

The study will be monitored by the sponsor on a regular basis throughout the study period.

During monitoring visits, the investigator will provide direct access to all source documentation relevant to the subject's participation in the study. Source documentation includes, but is not limited to, the subject's clinic and/or office chart, hospital chart, informed consent forms, treatment notes, laboratory reports, pharmacy records, radiographs, recorded data from automated instruments, and any other records maintained to conduct and evaluate the clinical study. The investigator must also ensure that direct access to study documents be made available for study-related audits, IRB review, or regulatory inspection.

18 QUALITY CONTROL AND QUALITY ASSURANCE

18.1 Data collection

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate and accurate case histories for the subjects treated under this protocol.

Case histories include CRFs and supporting data including, but not limited to, signed and dated informed consent forms, progress notes, hospital charts, nurse's notes, diary cards, laboratory reports, ECG strips, etc.

Subject demographics and key/essential disease baseline characteristics thought to affect outcome, i.e., stratification variables and other prognostic factors, will be collected, as available, for all subjects who provide written informed consent. For subjects who provide informed consent and were not entered/randomized into the study, the reason the subject was not entered/randomized, i.e., did not meet one or more inclusion criteria, met one or more exclusion criteria, or other (e.g., lost to follow-up, consent withdrawn), will also be collected.

18.2 Study monitoring

The primary source document for this study will be the subject's medical record. If separate research records are maintained by the investigator, both the medical records and the research records will be monitored/audited for the purposes of the study.

The investigator and institutions involved in the study will permit study-related monitoring and provide direct access to all study records and facilities. Adequate time and space for monitoring visits should be made by the investigator or other investigative site staff.

The monitor will visit study facilities at periodic intervals, in addition to maintaining necessary contact through telephone, e-mail, and letter. The monitor will assess subject enrollment and informed consent procedures; investigational product storage, dispensing, administration and accountability; compliance with protocol procedures; completeness and accuracy of data entered onto validated data collection instruments (paper CRF of electronic data screen) against original source documents; and the occurrence of AEs/SAEs. All aspects of the study will be carefully monitored for compliance with the protocol, applicable regulatory requirements, GCP, and the site's standard operating procedures.

The monitor will discuss the conduct and progress of the study with the investigator and other site staff. The investigator must cooperate with the monitor to ensure that corrective action is taken to resolve any problems noted in the course of the monitoring, and that the preventative measures are put into place to prevent recurrence of issues. In cases where compliance is not achieved, shipment(s) of investigational product to the investigator will be discontinued and study participation by that investigator will be terminated.

18.3 Audit and inspection of the study

During the conduct of the study, the sponsor or its representative may conduct audits of any data and any facility participating in the study. The investigator and institutions involved in the study will permit such study-related audits and provide direct access to all study records and facilities. The investigator must maintain a comprehensive and centralized filing system of all study-related documentation that is suitable for inspection by the sponsor or its designated monitors, auditors, IRB/IEC, or regulatory agency representatives. The investigator agrees to participate in audits conducted at a convenient time in a reasonable manner.

Government regulatory authorities from any of the country where the study is conducted may also perform inspections either during or after the study. In the event of an inspection by any regulatory authority, the investigator should promptly notify the sponsor. The investigator agrees to cooperate fully with inspections conducted by regulatory authorities and to allow representatives of the regulatory authority access to all study records. The investigator will forward to the sponsor a copy of any inspection records received.

19 PLANNED STUDY PERIOD

January 2014 to March 2018

20 END OF THE STUDY

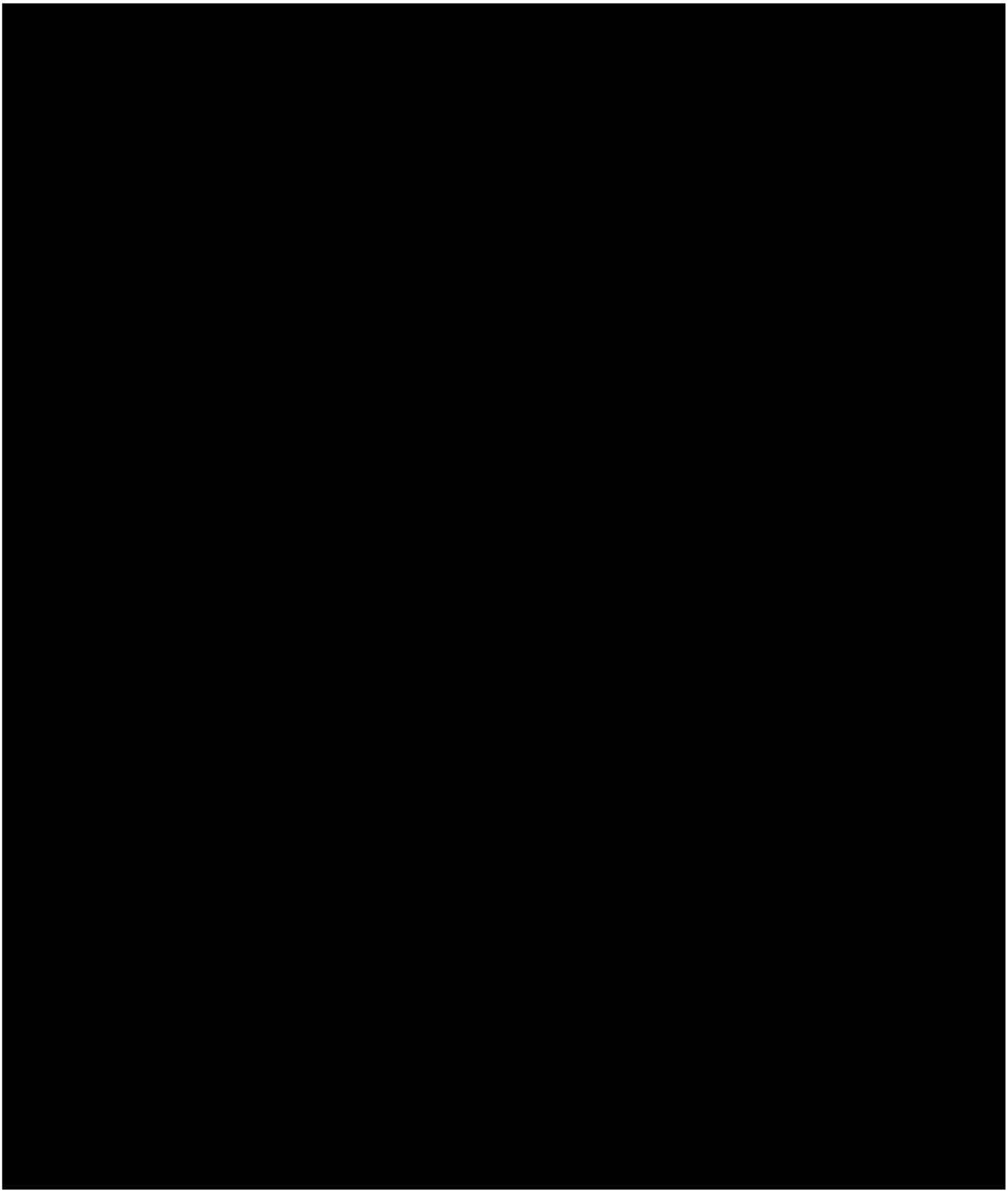
The end of the study ("study completion") is defined as the date of the last protocol-specified visit/assessment for all subjects in the study. All materials or supplies provided by the sponsor will be returned to the sponsor upon study completion. The investigator will notify the IRB when the study has been completed.

21 RECORD KEEPING

Study documents (including subject records, copies of data submitted to the sponsor, study notebook, and pharmacy records) must be kept secured until the date when relevant regulations stipulate in Japan or South Korea, whichever comes later. If the documents should be retained for a longer period than the regulation of the country where the organization exists, the sponsor will discuss the duration and method of archiving with the organization in responsible for archiving. The sponsor will inform the organization as to when these documents no longer need to be retained.

22 PUBLICATION POLICY

Publication by investigative site of any data from this study must be carried out with prior agreement of the sponsor.



APPENDICES/ATTACHMENTS

Appendix 1

MODIFIED BAUERMEISTER GRADING SCALE FOR RETICULIN*

Grade	Quantification of bone marrow reticulin and collagen
0	No reticulin fibers demonstrable
1	Occasional fine individual fibers and foci of a fine fiber network
2	Fine fiber network throughout most of the section; no coarse fibers
3	Diffuse fiber network with scattered thick coarse fibers but no mature collagen (negative to trichrome staining)
4	Diffuse, often coarse fiber network with areas of collagenization (positive trichrome staining)

* Adopted from Bauermeister, 1971; Bain et al, 2001

Appendix 2

APLASTIC ANEMIA WITH SEVERITY CRITERIA*

Classification	Criteria
Severe	BM cellularity < 25% (or < 50% if < 30% of BM is hematopoietic cells) AND ≥ 2 of the following: • Peripheral blood neutrophil count < $0.5x10^9$/L • Peripheral blood platelet count < $20x10^9$/L • Peripheral blood reticulocyte count < $20x10^9$/L
Very severe	As above, but peripheral blood neutrophil count must be < $0.2x10^9$/L
Nonsevere	Hypocellullar BM with peripheral blood values not meeting criteria for severe aplastic anemia

* Adopted from Guinan, 2011.

Appendix 3

GIMEMA BLEEDING SCALE*

Grade	Definition
0	No bleeding
1	Petechiae or mucosal bleeding, not requiring intervention
2	Melena, hematemesis, hematuria, hemoptysis
3	Bleeding requiring red blood cell transfusion
4	Retinal bleeding with visual impairment
5	Non-fatal cerebral bleeding
6	Fatal cerebral bleeding
7	Fatal non-cerebral bleeding

* Adopted and modified from Rubella et al., 1997