Public Title	Eltrombopag in MDS and AML with Thrombocytopenia
Scientific Title	A Phase I/II Study of Eltrombopag in Thrombocytopenic Subjects with Advanced Myelodysplastic Syndrome (MDS) or secondary Acute Myeloid Leukemia after MDS (sAML/MDS)
Short Title	Eltrombopag
Id KN/ELN	LN_DEUTSC_2010_332
Trialgoup	Deutsche MDS
Type of Trial	multicentric, randomized, double-blind, double-group
Phase	Phase I
Disease	Acute myeloid leukemia(AML) Supportive Care Myelodysplastic Syndrome(MDS) Intermedia II and high risk
Stage of Disease	.
Aim	- Safety and tolerability of eltrombopag - Effect of eltrombopag on platelet counts, on need for platelet transfusion, on duration of platelet transfusion independence, on bleeding events, on overall survival and to evaluate eltrombopag population pharmacokinetics.
Outcomes	- Safety and tolerability parameters incl. non-hematologic laboratory grade 3 and 4 toxicities, change in bone marrow blast counts from baseline and adverse vents reporting (Primary Outcome) - Proportion of subjects with: a baseline platelet count <20 Gi/L and an increase to > 20 Gi/L and by at least 2x baseline, or a baseline platelet count >20 Gi/L and an absolute platelet count increase to > 50 Gi/L at any time during treatment (unless in close connection to platelet transfusion); frequency and number of units of platelet transfusion during the treatment and follow-up; duration of platelet transfusion independence; incidence and severity of bleeding events during treatment and follow-up; overall-survival and eltrombopag population pharmacokinetic parameters and plasma concentration data.
Inclusion Criteria	- 1. Adult subjects (18 years of age or older) with advanced MDS or sAML/MDS with >/=20% and </=50% blasts in bone marrow, as well as peripheral blasts </=50% and absolute blasts <1 Gi/L. Both Type I and Type II blasts will be included in blast count - 2. Subjects must be dependent on regular platelet transfusions or have a platelet count taken within the 4 weeks prior to randomization that is <30 Gi/L - 3. Subjects must be relapsed, refractory or ineligible to receive standard treatment options of azacitidine and decitabine and must be relapsed, refractory or ineligible to receive intensive chemotherapy or autologous/allogeneic stem cell transplantation. - 4. Prior therapy with demethylating agents (azacitidine or decitabine), lenalidomide or IL-11(oprelvekin) must have been completed at least 4 weeks before Day 1; antithymocyte/antilymphocyte globulin, intensive chemotherapy, or autologous/allogeneic stem cell transplantation must have been completed at least 2 months before Day 1. - 5. Subjects must have platelet count and platelet transfusion data available over a period of 4 weeks prior to randomization. - 6. Subjects with MDS or sAML/MDS must have stable disease indicated by a doubling time of peripheral blast counts >7 days during screening. - 7. During the 4 weeks prior to randomization, subjects must have a baseline bone marrow examination including all of the following: - a. cytomorphology to confirm bone marrow blasts (Type I and Type II) between 20-50% - b. cytogenetics (provide only most prevalent abnormal clone), - c. histopathology,

- d. flow cytometric assessment of the megakaryocytic lineage markers CD41, CD61, and TPO-R.
- Flow cytometry may alternatively be performed on peripheral blood blasts provided that the subject has a sufficiently increased peripheral blood blast count (as per local flow cytometry requirements).
- 8. Supportive/palliative therapies such as cytokines (except for IL-11; oprelvekin), valproic acid, all-trans retinoic acid or mild chemotherapy are allowed if part of the local SOC, provided those therapies have been at a stable dose for 4 weeks or were completed 4 weeks prior to enrollment into this study. Erythropoiesis-stimulating agents (ESAs) in anemic subjects or granulocyte colony-stimulating factor (G-CSF) in subjects with severe neutropenia and recurrent infections are allowed during the study as per accepted standards. Subjects who enter the study on ESAs or G-CSF should continue at the same dose schedule until the optimal dose of study medication has been established.
- 9. ECOG Status 0-3.
- 10. Subject is able to understand and comply with protocol requirements and instructions.
- 11. Subject has signed and dated informed consent.
- 12. Prothrombin time (PT/INR) and activated partial thromboplastin time (aPTT) must be within 80 to 120% of the normal range at baseline.
- 13. The following clinical chemistries MUST NOT exceed the upper limit of normal (ULN) reference range by more than 50%: creatinine, ALT, AST, total bilirubin (except for Gilbert's Syndrome), and alkaline phosphatase. In addition, albumin must not be below the lower limit of normal (LLN) by more than 10%.
- 14. Subject is practicing an acceptable method of contraception (documented in chart). Female subjects (or female partners of male subjects) must either be of nonchildbearing potential (hysterectomy, bilateral oophorectomy, bilateral tubal ligation or post-menopausal >1 year), or of childbearing potential and use 1 of the following highly effective methods of contraception (i.e., Pearl Index <1.0%) from 2 weeks prior to administration of study medication, throughout the study, and 28 days after completion or premature discontinuation from the study:
- a. Complete abstinence from intercourse
- b. Intrauterine device (IUD);
- c. Two forms of barrier contraception (diaphragm plus spermicide, and for males condom plus spermicide);
- d. Male partner is sterile prior to entry into the study and is the only partner of the female; i.e. Systemic contraceptives (combined or progesterone only).

Exclusion Criteria

- 1. Subjects with a diagnosis of acute promyelocytic leukemia
- 2. History of treatment for cancer other than MDS or sAML/MDS with systemic chemotherapy and/or radiotherapy within the last 2 years.
- 3. History of treatment with romiplostim or other TPO-R agonists.
- 4. Pre-existing cardiovascular disease (including congestive heart failure, New York Heart Association [NYHA] Grade III/IV), or arrhythmia known to increase the risk of thromboembolic events (e.g. atrial fibrillation), or subjects with a QTc >450 msec (QTc >480 msec for subjects with Bundle Branch Block).
- 5. Bone marrow fibrosis that leads to an inability to aspirate marrow for assessment.
- 6. Spleen size >14 cm (length as per ultrasound examination).
- 7. Leukocytosis >/=25,000/uL prior to Day 1 of study medication.
- 8. Female subjects who are nursing or pregnant (positive serum or urine â-human chorionic gonadotropin [â-hCG] pregnancy test) at screening or pre-dose on Day 1.

	- 9. Current alcohol or drug abuse. - 10. Treatment with an investigational drug within 30 days or 5 half-lives (whichever is longer) preceding the first dose of study medication. - 11. Active and uncontrolled infections. - 12. Subjects infected with Hepatitis B, C or Human Immunodeficiency Virus (HIV).
Age	>= 18 years
Status	Closed
start of Recruitment	01.02.2010
Target Sample Size	60
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