1. Study Synopsis

Title of clinical trial	Efficacy and Safety of Eltrombopag in Patients with Acquired Moderate Aplastic Anemia (EMAA) who are treated with Ciclosporin A Prospective Randomized Multicenter Study comparing Thrombopoetin-Receptor agonist Eltrombopag (Revolade®, GlaxoSmithKline) with Placebo in Patients with Acquired Moderate Aplastic Anemia who are treated with Ciclosporin A
Protocol Short Title/Acronym	EMAA
Trial Phase	Phase II – III
Sponsor Details	University Hospital of Ulm, Albert-Einstein Allee 23, Ulm, Germany
Coordinating Investigator	Britta Höchsmann, Ulm, Germany & Hubert Schrezenmeier, Ulm, Germany
EudraCT number	2014-000174-19
Sponsor Protocol Code number	9345
Medical condition or disease under investigation	Moderate aplastic anemia
Purpose of clinical trial	The aim of this study is to improve treatment of Moderate Aplastic Anemia (MAA) by evaluating the safety and efficiency of Eltrombopag as a new treatment option in patients with therapy requiring MAA.
Primary objective	The primary objective of this trial is the evaluation of the superiority of Eltrombopag on top of background treatment with Ciclosporin (CSA) regarding hematologic response (PR + CR) at 6 months in comparison with treatment with CSA alone in untreated MAA patient.
Secondary objective (s)	The secondary objective of this trial is to investigate the impact of Eltrombopag added to background therapy with CSA therapy on all outcome measures, safety and quality of life in untreated AA patients. As well as the evaluation of telomere lengths and telomerase mutations as biomarkers for response on Eltrombopag therapy in MAA and the evaluation of the new Aplastic Anemia and Paroxysmal Nocturnal Hemoglobinuria (PNH) specific quality of life questionnaire QLQ-AA/PNH. Secondary endpoints are: • Trilineage (CR and PR) and single lineage hematological response rate at 3, 6, 12 and 18 months. • cumulative incidence of response • time to best hematological and single lineage response • proportion of patients with need for transfusions and number of units transfused (PRBC and PC) since start of treatment • cumulative incidence of progress to SAA/VSAA or intensive immunosuppressive treatment with ATG

	• toxicity profile as measured using the CTCAE criteria • relapse rate at 6, 12 and 18 months • cumulative incidence of relapse (from best trilineage hematological response) • overall survival • failure-free survival • telomere lengths and presence of telomerase mutations as biomarkers for response. • quality of life as assessed by quality of life instruments (FACIT-F SCALE and EORTC QLQ-C30, in some countries in addition with the QLQ-AA/PNH) • Pharmacokinetic studies for assessment of dose dependency regarding efficiency and safety in a part of the patients
Trial Design	This is a prospective, randomized, placebo-controlled, double-blind multicenter study.
Risk Benefit Analysis	There is a lack of efficient therapeutic options with tolerable toxicity profiles for patients with Aplastic Anemia (especially elderly patients). Due to lack of treatments with few side effects the current treatment policy for this group of patients often comprises only supportive therapy. Thus, there is a strong need for efficient and non-toxic therapeutic strategies due to the risk of cytopenia and resulting infections or bleedings as well as a known reduced quality of life in patients with MAA. The thrombopoetin receptor agonist Eltrombopag (Revolade®) is an approved drug for adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) in splenectomized patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins). In August 2014 Eltrombopag (Revolade®) has been approved for Severe Aplastic Anemia refractory to immunsuppressive therapy by the FDA. This decision was based on a recently published phase II study which investigated Eltrombopag as single agent treatment in patients with AA refractory to immunsuppressive treatment with ATGAM® / CSA. Forty-four percent of patients had a hematological response in at least one lineage at 12 weeks. Eltrombopag was well tolerated. Some patients even achieved bi- or trilineage response. The increase in blood counts, in particular platelet count, occurred over several months, i.e. in AA patients kinetics of response to Eltrombopag is delayed compared to patients with immune thrombocytopenia. Factors that predicted a response to Eltrombopag were less depressed baseline reticulocytes and immature platelet count. This may reflect residual stem cells which can respond to Eltrombopag. If this is true, the chance for response might be even better in MAA which is characterized by a less depleted stem / progenitor cell compartment. Additionally, we hypothesize that there might be a higher rate of patients responding to Eltrombopag in a group of therapy naïve patients with Aplastic Anemia, especially in Moderate Aplastic Anemia. We assess the risk of adverse events and unwanted side effects as containable because the drug was well tolerated in the mentioned study regarding Eltrombopag in refractory SAA as well as in refractory ITP in which it is approved for use since 2008 in the United States and 2010 in Europe. Furthermore

	there was no hint for an additive hepatotoxicity by the addition of Eltrombopag to hATG/CSA in interim analyses of an ongoing trial in SAA/VSAA (NIH12-H-0150). Thus, in our opinion the possible benefit of Eltrombopag as a new therapeutic option in patients with Aplastic Anemia clearly overweighs the potential risk of this treatment. Finally, this study is needed in order to clarify the role of Eltrombopag within standard treatment of Aplastic Anemia, especially in Moderate Aplastic Anemia
Endpoints	1. The primary endpoint of the study is the hematologic response rate (CR + PR) at 6 months. 2. Secondary endpoints are: • Trilineage hematological response rate (CR and PR) at 3, 6, 12 and 18 months. • single lineage response at 3, 6, 12 and 18 months • cumulative incidence of response • time to best hematological and single lineage response • proportion of patients with need for transfusions and number of units transfused (PRBC and PC) since start of treatment • cumulative incidence of progress to SAA/VSAA or intensive immunosuppressive treatment with ATG • toxicity profile as measured using the CTCAE criteria for patients receiving placebo in comparison to patients receiving eltrombopag, both on top of background treatment with CSA • relapse rate at 6, 12 and 18 months • cumulative incidence of relapse (from best hematological response) • overall survival • failure-free survival • telomere lengths and presence of telomerase mutations as biomarkers for response. • quality of life as assessed by quality of life instruments (FACIT-F SCALE and EORTC QLQ-C30, partly in addition with the QLQ-AA/PNH)
Approximate number of patients required	The required number of patients evaluable for statistical analysis is 116 (58 each group)
Summary of inclusion criteria	Diagnosis of Moderate Aplastic Anemia without prior specific therapy and an indication for CSA treatment MAA is defined as Aplastic Anemia fulfilling the following criteria: • no evidence for other disease causing marrow failure • hypocellular bone marrow for age • depression of at least two out of three peripheral blood counts below the normal values: o absolute neutrophil count (ANC) <1.2 G/L o platelet count < 70 G/L o absolute reticulocyte count < 60 G/L without fulfilling the criteria for SAA

	In this study need for treatment with CSA is defined as: a) transfusion-independent MAA and: ANC < 1.0 G/L or hemoglobin < 8.5 g/dl and reticulocyte count < 60 G/L or platelet count < 30 G/L or significant clinical symptoms (infections, bleeding, anemia) b) transfusion-dependent moderate aplastic anemia Platelet transfusion dependency is defined as prophylactic transfusion (platelet counts < 10 G/L with no bleeding) or therapeutic transfusion Red cell transfusion dependency is defined as transfusion of at least 4 units of packed red blood cell concentrates (PRBC) in the 12 weeks prior to study entry A signed and dated informed consent.
Summary of exclusion criteria	1. Age < 18 years 2. Severe or Very Severe Aplastic Anemia (hypocellularity of bone marrow 25% and depression of two of the three peripheral counts: ANC < 0.5 G/L, platelet count < 20 G/L, reticulocyte count < 20 G/L) 3. Constitutional Aplastic Anemia (i.e. Fanconi anemia or Dyskeratosis congenita) 4. Clonal myeloid disorders based on cytogenetic findings performed within 12 weeks of study entry. Especially patients with cytogenetic abnormalities which are recurrent in MDS are not eligible for the study. 5. Bone marrow reticulin fibrosis of grade 3 or greater 6. Severe concurrent diseases precluding the patient's ability to tolerate protocol therapy 7. ALT > 3 times the upper limit of normal if this elevation is progressive, or persistent for 4 weeks, or accompanied by increased direct bilirubin, or accompanied by clinical symptoms of liver injury or evidence for hepatic decompensation 8. Infection not adequately responding to appropriate therapy 9. HIV-positivity (patients with Hepatitis B or Hepatitis C are only in combination with hepatic failure (see criteria 7) excluded) 10. Moribund status with a likely death within 3 months 11. History of malignancy other than localized tumors diagnosed more than one year previously and treated surgically with curative intent (for instance squamous cell or other skin cancers, stage 1, breast cancer in situ, cervical carcinoma in situ...). 12. Prior specific treatment of Aplastic Anemia with immuno-suppression or androgens or interleukin2-receptor-antibodies. The use of these drugs in context of other disorders before diagnosis of aplastic anemia is not an

	exclusion criteria if these treatments were finished longer than 6 months before study entry. 13. Treatment with other hematological effective drugs (including erythropoetin) within 3 months before study entry as well as treatment with corticosteroids and G-CSF within 3 weeks before enrollment 14. Known hypersensitivity to Eltrombopag or its components 15. Known hypersensitivity to Ciclosporin 16. Current nursing, pregnancy, or unwillingness to take oral contraceptives or use a barrier method of birth control to refrain from pregnancy as well as a missing or positive pregnancy test within the last 14 days before inclusion for women of childbearing potential during the course of this study 17. Inability to understand the investigational nature of the study or to give informed consent. 18. Renal failure with creatinine > 2× upper limit of normal. 19. Uncontrolled hypertension 20. Participation in any study using an investigational drug or treatment with an investigational drug within 30 days preceding the first dose of study medication
Therapy/Intervention	Patients are double-blinded randomized to receive either Eltrombopag or placebo on top of the background therapy with CSA Eltrombopag is given at a daily starting dose of 150 mg orally with the option of dose escalation or reduction regarding hematologic response. Scheduled unblinding after reaching the primary study endpoint (6 months after start of study treatment). Details see trial treatment plan
Maximum treatment duration within the study	18 months from first day of treatment
Definition of the end of the Trial	Last patient last visit
End of Follow up	24 months after the end of study medication
Statistical Plan	Baseline response (PR+CR) expectation after 6 months with standard immunosuppression with CSA alone is 46% (Marsh et al 1999)[2] : The sample size is calculated on the hypothesis that in the experimental arm the addition of Eltrombopag will increase the 6-months response rate (CR + PR) up to 71%. In these conditions, for a targeted power of 80 % and at a 5% significance level (two-sided test) a number of n = 116 evaluable patients (58 each group Eltrombopag/Placebo) is required. After applying a correction for a loss to follow-up rate of 5%, 122 patients (61 each group Eltrombopag/Placebo) have to be accrued.The chi-square test will be used to compare categorical variables, and the Mann-Whitney U test (nonparametric) or student t-test (parametric) will be used to compare continuous variables. The probability of response and survival will be analyzed using the method of Kaplan and Meier and log rank test. A logistic regression of binary outcomes will provide results with respect to the relevant covariates (disease severity, age). A significance level of 5% will be used for all explorative analyses. Sample size calculation for a superiority trial with binary outcome

	based on the formula: $n = f(a/2, ax \{p1 \times (100-p1) + p2 \times (100 - p2)\} / (p2-p1)^2$ p1 and p2 are the percent “success” in the control and experimental group respectively. Eltrombopag