Synopsis

Rationale	Mutations in isocitrate dehydrogenase 1 (*IDH1)* and isocitrate dehydrogenase 2 *(IDH2)* are observed in approximately 20% of patients with newly diagnosed AML (cumulative percentage for both mutations). The rationale of the current study is that addition of drugs specifically designed to target leukemias harboring these mutations may improve treatment outcome in newly diagnosed patients when combined with standard induction and consolidation therapy and when given as maintenance therapy thereafter. The drugs investigated in this study are ivosidenib (AG-120) and enasidenib (AG-221), which are potent inhibitors of the IDH1 and IDH2 mutant proteins, respectively.
Study objectives	Primary: - To compare event-free survival (EFS) between ivosidenib/enasidenib and placebo in combination with induction therapy and consolidation therapy followed by maintenance therapy in patients with newly diagnosed acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) with excess blasts-2 (EB2), with an *IDH1* or *IDH2* mutation, eligible for intensive chemotherapy. Key secondary objective: - To determine if treatment including ivosidenib/enasidenib, as compared to placebo, prolongs overall survival (OS). Other secondary objectives: - To compare relapse-free survival (RFS), cumulative incidence of relapse (CIR) and cumulative incidence of death (CID) after complete response (CR) and CR with incomplete hematologic recovery (CRi) between treatment including ivosidenib/enasidenib and treatment including

	placebo. - To evaluate minimal residual disease (MRD) status at sequential time points throughout treatment and CR_{MRD-} rates between treatment including ivosidenib/enasidenib vs. placebo, using molecular and/or flow cytometric techniques. - To assess the safety and tolerability of treatment including ivosidenib/enasidenib vs. placebo. - To compare CR/CRi rates for treatment including ivosidenib/enasidenib vs. placebo. - To assess the time to hematopoietic recovery (ANC 0.5 and $1.0x10^9$/l; platelets 50 and $100x10^9$/l) after each chemotherapy treatment cycle. - To determine quality of life (QoL) during maintenance treatment with ivosidenib/enasidenib vs. placebo. Exploratory objective: - To study the pharmacokinetics of treatment including ivosidenib/enasidenib in a small subset of patients.
Study design	Prospective, multicenter, double-blinded, randomized, placebo-controlled phase 3 clinical study.
Patient population	Newly diagnosed patients ≥18 years of age with AML or MDS-EB2 with a mutation in either *IDH1* or *IDH2*, considered eligible for intensive treatment.
Intervention	Based on the assessment of *IDH1* or *IDH2* mutations, patients will be randomized to receive one of the investigational drugs, ivosidenib or enasidenib, or a placebo in combination with standard induction and consolidation treatment. After completing induction and consolidation treatment, patients will receive maintenance therapy with the investigational drug or placebo according to the initial randomization.
Duration of treatment	Patients will receive an induction treatment for 2 cycles,

	followed by consolidation treatment. Expected duration of induction treatment is approximately 3 months. Consolidation will take an additional 1-3 months. Maintenance treatment after the consolidation phase will be given for up to two years from the start of maintenance. Subsequently, patients will be followed for 10 years after randomization.
Target number of patients	968 patients in total (484 patients with an *IDH1* mutation and 484 patients with an *IDH2* mutation)
Expected duration of accrual	4 years
Main study endpoints	Primary endpoint: - Event-free survival (EFS) Key secondary endpoint: - Overall survival (OS) Other secondary endpoints: - Relapse-free survival (RFS**)** after CR/CRi - Cumulative incidence of relapse (CIR) after CR/CRi - Cumulative incidence of death (CID) after CR/CRi - Complete remission without minimal residual disease (CR_{MRD-}) rate after induction cycle 2 - Frequency and severity of adverse events according to CTCAE version 5.0 - CR/CRi rates after induction cycle 1 and 2 - CR/CRi rate after remission induction (i.e., CR or CRi as best response during or at completion of induction therapy) - Time to hematopoietic recovery after each chemotherapy treatment cycle - EQ-5D-5L visual analogue scale (VAS), - EORTC-QLQ-C30 global health status/QoL scale.

Benefit and nature and extent of the burden and risks associated with participation	Treatment outcomes for patients with AML or MDS-EB2 with *IDH1* or *IDH2* mutations treated with current standard of care including intensive chemotherapy are unsatisfactory. The selective oral IDH inhibitors ivosidenib and enasidenib have shown promising anti-leukemic activity in phase 1/2 clinical trials in patients with *IDH1* or *IDH2* mutations, respectively. When added to current treatment regimens, these inhibitors can potentially prevent relapse and improve long term outcome. The potential undesirable effects of ivosidenib and enasidenib in humans based on recent clinical studies are summarized in Section 9.7 and 9.8. Patients will have adequate and appropriate monitoring during the study to monitor for AEs and to minimize risk. The independent Data Safety Monitoring Board (DSMB) will perform review of the data as documented in the protocol and DSMB Charter. The potential risks identified from non-clinical and clinical studies are judged to be acceptable in light of the potential benefits. Strict adherence to the eligibility criteria is essential to ensure that appropriate patients are selected for participation. Equally important is strict adherence to the schedule of safety assessments to ensure that patients are appropriately monitored.
Planned interim analysis and DSMB	Several interim analyses for safety and efficacy will be performed as described in section 14. A DSMB consisting of independent experts with expertise in clinical trial statistics and leukemia treatment will be installed for review of the interim analyses as well as annual progress and annual safety information. See section 12.10 and 14.2.4 for more details.