Final Report of the Trial AMLSG 24-15

Title	A Phase II Study with a Safety Run-in Phase Evaluating Vosaroxin With Azacitidine in Older Patients with Newly Diagnosed Acute Myeloid Leukemia and Intermediate/Adverse Genetic Risk or Myelodysplastic Syndrome with Excess Blasts-2 (MDS-EB-2)
Project Code	AMLSG 24-15
Active Substances/Finished Products	Vosaroxin Azacitidine (Vidaza®)
Protocol Number	Vosaroxin_18Jan2018_V1.3
Positive Vote of the Ethics Committee	26.03.2018
Termination of the Trial	31.10.2019 (prematurely)
Sponsor	University Hospital of Ulm, represented by the Chairman of the Board
EudraCT Number	2015-004066-28

1. Name of Sponsor/Company

1.1 Sponsor

Ulm University Hospital, represented by the Chairman of the Board

Address:
Universitätsklinikum Ulm
Albert-Einstein-Allee 29
D-89081 Ulm

1.2 Organisation/Management

Coordinating Investigator Germany (Leiter der Klinischen Prüfung)	PD Dr. Verena Gaidzik Ulm University Hospital Albert-Einstein-Allee 23 89081 Ulm Germany
Clinical Trials Office	AMLSG Clinical Trials Office Ulm University Hospital Albert-Einstein-Allee 23 89081 Ulm Germany
Central clinical laboratories	AMLSG Laboratory for Molecular and Cytogenetic Diagnostics (Ulm) Prof. Dr. Konstanze Döhner, Prof. Dr. Hartmut Döhner Ulm University Hospital Department of Internal Medicine III Laboratory for Molecular and Cytogenetic Diagnostics Albert-Einstein-Allee 23 89081 Ulm Germany AMLSG Laboratory for Molecular Diagnostics (Hannover) Prof. Dr. A. Ganser, Prof. Dr. Michael Heuser, Prof. Dr. Felicitas Thol Hannover Medical School Department of Hematology, Hemostaseology, Oncology and Stem Cell Transplantation Carl-Neuberg-Strasse 1 30625 Hannover Germany
Central clinical laboratories	AMLSG Laboratory for Cytogenetic Diagnostics (Hannover) Prof. Dr. B. Schlegelberger Hannover Medical School Institute for Cellular and Molecular Pathology Carl-Neuberg-Str. 1 30625 Hannover Germany

Monitoring	Alcedis GmbH Winchesterstr. 3 35394 Gießen (Europaviertel) Germany
Data Management	AMLSG Clinical Trials Office Ulm University Hospital Albert-Einstein-Allee 23 89081 Ulm Germany
Statistician	Axel Benner German Cancer Research Center Division of Biostatistics Im Neuenheimer Feld 280 69120 Heidelberg Germany

2. Name of Finished Product

Vosaroxin

Vidaza®

3. Name of Active Substance

Vosaroxin

Azacitidine

4. Individual Study Table

Not applicable

5. Title of Study

A Phase II Study with a Safety Run-in Phase Evaluating Vosaroxin With Azacitidine in Older Patients with Newly Diagnosed Acute Myeloid Leukemia and Intermediate/Adverse Genetic Risk or Myelodysplastic Syndrome with Excess Blasts-2 (MDS-EB-2)

(AMLSG 24-15)

Initial approved version of study protocol:
Vosaroxin_18Jan2018_V1.3

Amendments of the protocol:
No amendments of the protocol were performed.

6. Investigators

Investigator	Site
Prof. Dr. Maike de Wit	Vivantes Klinikum Berlin-Neukölln
Prof. Dr. Wolff Schmiegel	Knappschaftskrankenhaus Bochum
Prof. Dr. Dominik Wolf	Universitätsklinikum Bonn
Dr. Mohammed Wattad	Kliniken Essen-Süd Evang. Krankenhaus Essen-Werden gGmbH
Prof. Dr. Nadezda Basara	Malteser Krankenhaus St. Franziskus-Hospital
Dr. Martin Mikusko	Universitätsklinikum der Otto-von-Guericke Universität Magdeburg
Prof. Dr. Doris Kraemer	Klinikum Oldenburg
PD Dr. Simone Thomas	Universitätsklinikum Regensburg
Prof. Dr. Jochen Greiner	Diakonie-Klinikum Stuttgart
PD. Dr. Marcus Schittenhelm	Medizinische Universitätsklinik Tübingen
Coordinating investigator: PD Dr. Verena Gaidzik	Universitätsklinikum Ulm

7. Study centres

Site address
Vivantes Klinikum Neukölln Innere Medizin Hämatologie und Onkologie Rudower Str. 48 12351 Berlin
Medizinische Universitätsklinik Knappschaftskrankenhaus Bochum In der Schornau 23-25 44892 Bochum
Universitätsklinikum Bonn Medizinische Klinik und Poliklinik III Sigmund-Freud-Str.25 D-53105 Bonn
Kliniken Essen-Süd Evang. Krankenhaus Essen-Werden gGmbH Zentrum f. Innere Medizin, Hämatologie, internistische Onkologie u. SZT Pattberg 1-3 D-45239 Essen
Malteser Krankenhaus St. Franziskus-Hospital Medizinische Klinik I Waldstr. 17 24939 Flensburg
Universitätsklinikum der Otto-von-Guericke Universität Magdeburg Klinik für Hämatologie und Onkologie Leipziger Str. 44 39120 Magdeburg
Klinikum Oldenburg Klinik für Innere Medizin II Rahel-Straus-Str. 10 26133 Oldenburg
Universitätsklinikum Regensburg Klinik für Poliklinik für Innere Medizin III Franz-Josef-Strauß-Allee11 93053 Regensburg
Diakonie-Klinikum Stuttgart Rosenbergstraße38 D-70176 Stuttgart
Medizinische Universitätsklinik Tübingen Innere Medizin II Otfried-Müller-Str. 10 D-72076 Tübingen
Universitätsklinikum Ulm Klinik für Innere Medizin III Albert-Einstein-Allee 23 D-89081 Ulm

8. Publication reference

No publication planned.

9. Studied period

First patient in:	14.05.2018
Last patient last visit:	31.10.2019 (premature termination of the trial by the pharmaceutical company SUNESIS Pharmaceuticals, Inc due to discontinuation of the corresponding development program of the investigational drug vosaroxin)

There was no interruption of recruitment.

10. Phase of Development

Phase II

11. Objectives

Primary Efficacy Objective

- To evaluate the activity of vosaroxin in combination with azacitidine on the rate of complete remission (CR) and CR with incomplete blood count recovery (CRi)

Key Secondary Efficacy Objective

- To conduct a pre-defined subgroup analysis in patients with complex karyotype to evaluate the activity of vosaroxin in combination with azacitidine on CR and CRi

Secondary Efficacy Objectives

- To evaluate the rate of CR and rate of combined CR/CRi and CR with negativity for minimal residual disease (CR_{MRD-})
- To analyze the duration of response (DOR)
- To evaluate event-free survival (EFS)
- To evaluate overall survival (OS)

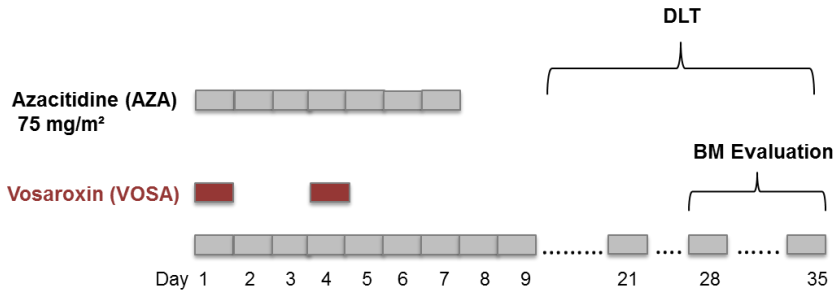
12. Methodology

Study Design

The main part of this trial was planned as a phase II study of vosaroxin with azacitidine in older patients with newly diagnosed AML and intermediate or adverse genetic risk or MDS-EB-2. An initial safety run-in phase was planned to be performed administering the study drug vosaroxin with azacitidine in up to 18 patients to determine the vosaroxin dose for the phase II part which was planned to include 150 patients in total.

Treatment

Safety run-in phase:



The initial safety run-in phase of the study was planned to evaluate the feasibility and toxicity of vosaroxin in combination with the hypomethylating agent azacitidine. The initial dose of vosaroxin in the treatment cycle was 70 mg/m^2 on days 1 and 4. Azacitidine was given in the dose of 75 mg/m^2/d on days 1 to 7.

A standard 3+3 design was used. Vosaroxin dose levels were defined at level "0" of 70 mg/m^2 as the initial dose, level "-1" of 50 mg/m^2, and level "-2" of 40 mg/m^2. If more than one DLT would occur with the actual vosaroxin dose, the dose of vosaroxin would be de-escalated. Recruitment would be conducted until 6 patients are treated at one dose level without observed DLT. If no DLT occured in 6 patients, then this dose level would be used for phase II. The dose limiting toxicity (DLT) period was up to 35 days. This interval allowed patients to proceed to next treatment cycle without delay. Patients participating in the safety run-in phase at the final dose continued according to the phase II part of the protocol.

Dosage and treatment in the phase II part of the study:

According to the original study protocol patients were to receive up to 8 cycles of azacitidine and vosaroxin. In each treatment cycle patients would receive azacitidine at 75 mg/m^2/d subcutaneously on days 1-7 and vosaroxin intravenously at day 1 and 4. The vosaroxin dose was planned to be determined during the preceding safety run-in phase, but would not exceed 70 mg/m^2/d on days 1 and 4 in each treatment cycle. Cycles would be repeated every 4 to 6 weeks.

After 1st cycle, azacitidine could be administered on days 1-7 or, in case of logistical difficulties at the weekend, on days 1-5, and 8-9. In case of unresolved toxicity after the 1st or 2nd cycle, patients would be allowed to proceed directly to maintenance therapy once the toxicity returns to CTC ≤1°.

Response assessment including bone marrow evaluation was planned to be performed after cycle 1, 2, 4, 6 and 8; patients achieving CR, CRi, PR or having stable disease (SD) would be eligible for subsequent cycles; only patients with clear evidence of progressive disease (PD) would be taken off protocol.

Following a maximum of 8 treatment cycles with azacitidine and vosaroxin, patients would receive maintenance therapy with single agent azacitidine; azacitidine would

be administered every 4 to 6 weeks on days 1-7 or, in case of logistical difficulties at the weekend, on days 1-5, and 8-9.

Allogeneic hematopoietic cell transplantation (HCT):

Patients could be assigned to allogeneic HCT at any time during treatment following at least two cycles of azacitidine and vosaroxin. Assignment would be primarily based on established risk scores. The disease should preferably be in remission. Conditioning regimens could be selected according to institutional standards.

13. Number of patients (planned and analyzed)

Number of patients initially planned: 150

Number of patients recruited: 9

Number of patients analyzed: 9

Nine patients were recruited within the initial safety run-in phase at four of the eleven participating investigator sites in Germany.

14. Diagnosis and main criteria for inclusion/exclusion

Diagnosis: Acute Myeloid Leukemia or Myelodysplastic Syndrome with Excess Blasts-2 (MDS-EB-2)

Main Inclusion Criteria:

1. Patients with confirmed diagnosis of acute myeloid leukemia (WHO 2016) and intermediate or adverse genetic risk (according to 2017 ELN recommendations); or patients with myelodysplastic syndrome with excess blasts-2 (MDS-EB-2)
2. Patients ≥60 years of age
3. No prior chemotherapy for leukemia except hydroxyurea to control hyperleukocytosis for up to 10 days during the diagnostic screening phase; patients may have received prior therapy for myelodysplastic syndrome different from hypomethylating agents
4. ECOG performance status ≤2
5. Men must use a latex condom during any sexual contact with women of childbearing potential, even if they have undergone a successful vasectomy and must agree to avoid to father a child (while on therapy and for 3 month after the last dose of vosaroxin)
6. Non-pregnant and non-nursing women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test within a sensitivity of at least 25 mIU/mL within 72 hours prior to registration (“Women of childbearing potential” is defined as a sexually active mature woman who has not undergone a hysterectomy or who has had menses at any time in the preceding 24 consecutive months).

7. Female patients of reproductive age must agree to avoid getting pregnant while on therapy and for 3 months after the last dose of vosaroxin.
8. Women of child-bearing potential including the female partners of the male patients must either commit to continued abstinence from heterosexual intercourse or apply two acceptable methods of birth control (IUD, tubal ligation, or partner's vasectomy). Hormonal contraception is an inadequate method of birth control.
9. Men must use a latex condom during any sexual contact with women of childbearing potential, even if they have undergone a successful vasectomy (while on therapy and for three months after the last dose of chemotherapy)
10. Willing to adhere to protocol specific requirements
11. Following receipt of verbal and written information about the study, the patient must provide signed informed consent before any study related activity is carried out

Main Exclusion Criteria:

1. Known or suspected hypersensitivity to the study drugs and/or any excipients
2. Favorable genetics: t(15;17)(q22;q12), *PML-RARA*; t(8;21)(q22;q22), *RUNX1-RUNX1T1*; inv(16)(p13.1q22)/t(16;16)(p13.1;q22), *CBFB-MYH11*; mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}
3. Prior treatment for AML except hydroxyurea
4. Prior treatment for MDS with hypomethylating agents
5. ECOG performance status >2
6. Patients who are not eligible for intensive chemotherapy
7. Inadequate cardiac, hepatic and/or renal function at the Screening Visit defined as:
   - Ejection fraction <40% confirmed by echocardiography
   - Creatinine >1.5x upper normal serum level
   - Total bilirubin, AST or ALT >1.5 upper normal serum level
8. Active central nervous system involvement
9. Any clinically significant, advanced or unstable disease or history of that may interfere with primary or secondary variable evaluations or put the patient at special risk, such as:
   - Myocardial infarction, unstable angina within 3 months before screening
   - Heart failure NYHA III/IV
   - Severe obstructive or restrictive ventilation disorder
   - Uncontrolled infection
10. Severe neurological or psychiatric disorder interfering with ability of giving an informed consent
11. Currently receiving a therapy not permitted during the study, as defined in Section 10.5.4 of the protocol

12. Patients with a “currently active” second malignancy other than non-melanoma skin cancers. Patients are not considered to have a “currently active” malignancy if they have completed therapy and are considered by their physician to be at less than 30% risk of relapse within one year.
13. Known history of positive test for Hepatitis B surface Antigen (HBsAg) or hepatitis C antibody or history of positive test for Human Immunodeficiency Virus (HIV)
14. Hematological disorder independent of leukemia
15. No consent for registration, storage and processing of the individual disease characteristics and course as well as information of the family physician and/or other physicians involved in the treatment of the patient about study participation
16. No consent for biobanking
17. Current participation in any other interventional clinical study within 30 days before the first administration of the investigational product or at any time during the study
18. Patients known or suspected of not being able to comply with this trial protocol
19. Patients of childbearing potential not willing to use adequate contraception during study and 3 months after last dose of therapy
20. Breast feeding women or women with a positive pregnancy test at Screening visit

15. Test product, dose and mode of administration, batch number

The Investigational Products (IMPs) in this study were vosaroxin and azacitidine (Vidaza®).

Vosaroxin was supplied in 25-mL vials. Each vial contained 230 mg vosaroxin at a concentration of 10 mg/mL. Vosaroxin was administered in each treatment cycle on day 1 and day 4, IV over ten minutes. Within the safety run-in phase the following dose levels were used to evaluate and determine the dose for the phase-II part of the trial.

Dose level	Vosaroxin dose
Dose level 0	70 mg/m^2
Dose level -1	50 mg/m^2
Dose level -2	40 mg/m^2

Vosaroxin was supplied by Sunesis Pharmaceuticals, Inc. to the Central Pharmacy of Ulm University Hospital. Study drug for individual patients was shipped from the Central Pharmacy of Ulm University Hospital to the pharmacy at the study site.
The following batch number was used: B170001.

Azacitidine (Vidaza®) was given in the dose of 75 mg/m^2/d on days 1 to 7.

It was not provided free-of-charge by the sponsor. It was supplied by the pharmacy of the participating site as commercial drug. Batch numbers therefore are not applicable. Azaciticine commercially is provided as powder for injection as subcutaneous use, at a concentration of 25mg/ml.

16. Duration of treatment

The estimated treatment duration of an individual patient enrolled into the trial was 12 months. Patients were intended to receive up to 8 treatment cycles of azacitidine and vosaroxin. After completion of 8 cycles, patients were planned to be scheduled to maintenance with single agent azacitidine at 75 mg/m²/d on days 1-7 until relapse or progression. Follow-up period was planned until 3 years after last patient in.

17. Reference therapy, dose and mode of administration, batch number

Not applicable.

18. Criteria for evaluation: Efficacy, Safety

The frequency and timing of efficacy and safety measurements were defined in the study protocol.

Efficacy Measurements

Efficacy assessments were done after cycle 1, 2, 4, 6 and 8 and thereafter during maintenance therapy every 3 months or if relapse was suspected. They were based on analysis of full blood count and bone marrow aspirate. Only for patients with hematological response (CR, CRi, PR) the status/presence of extramedullary lesions had to be evaluated by the time of bone marrow (BM) evaluation by imaging-based techniques (e.g. conventional computerized tomography (CT), spiral CT scan or magnetic resonance imaging (MRI)).

The response to treatment of AML and MDS-EB2 was evaluated using standard criteria. For AML response criteria were adapted from Döhner H, Estey E, Grimwade D, et al. Diagnosis and Management of Acute Myeloid Leukemia in Adults: 2017 Recommendations from an International Expert Panel, on Behalf of the European LeukemiaNet. Blood. 2016 Nov 28 (see Appendix A).

For MDS-EB2 response criteria were used in adaption from Bruce D. Cheson, Peter L. Greenberg, John M. Bennett, Bob Lowenberg, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood.2006;108:419-425 (see Appendix B).

The response at every assessment time point was recorded for all patients.

Primary Efficacy Variable

The primary efficacy variable for this trial was the rate of complete remission (CR) and CR with incomplete blood count recovery (CRi).

Secondary Efficacy Variables

The key secondary efficacy variable for this trial was the rate of CR and CRi in a pre-defined subgroup analysis in older (≥60 years) patients with complex karyotype after combined therapy of vosaroxin with azacitidine

Further secondary efficacy variables were:

- Rate of CR and rate of combined CR/CRi and CR with negativity for minimal residual disease (CR_{MRD-})
- Duration of response (DOR)
- Event-free survival (EFS)
- Overall survival (OS)

Quality of Life Endpoint

- Quality of life assessed by the EORTC Quality of Life Core Questionnaire (QLQ-C30), supplemented by information on self-assessed concomitant diseases, late treatment effects, and demographics [Messerer et al.] at the Screening visit, after each treatment cycle, at the end of treatment visit and at the last follow-up visit.

Safety Measurements

In this study, safety was assessed by evaluating the following: reported adverse events, clinical laboratory test results, vital signs measurements, ECG findings, chest X-Ray, echo scan, physical examination findings, monitoring of concomitant therapy. For each safety parameter, all findings (whether normal or abnormal) were recorded in the eCRF.

Adverse events were coded and graded using the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03 of the US National Cancer Institute (http://ctep.info.nih.gov/reporting/ctc.html).

Safety Endpoint Variables

Safety endpoint variables for this trial were:

- To determine safety and feasibility of the combination of vosaroxin with azacitidine
- 30-day and 60-day mortality
- Incidence and intensity of adverse events (AEs) according to Common Terminology Criteria for Adverse Events (CTCAE) version v4.03

19. Statistical methods

Safety run-in phase:

Primary safety endpoint of the safety run-in phase was DLT (dose-limiting toxicity), not attributable to persisting leukemia.
A standard 3+3 design was used. Vosaroxin dose levels were defined at level “0” of 70 mg/m^2 as the initial dose, level “-1” of 50 mg/m^2, and level “-2” of 40 mg/m^2.

The following dose de-escalation rules were used to enter patients at the three dose levels:

- Three patients will be enrolled sequentially on a dose level, starting from dose level “0”.
- If no DLT is observed in 3 patients, then the same dose will be used in the following cohort of 3 patients.
- If 1 of 3 patients experiences DLT at the current dose, then up to 3 more patients will be accrued at the same dose level. If none of these 3 additional patients experience DLT, then this dose level will be used for phase II. If 1 or more of these 3 additional patients experiences DLT, the MTD has been exceeded and 3/6 more patients will be treated in the next lower dose.
- Thus, if 2 or more patients in the same cohort encounter DLT, then the MTD has been exceeded and 3/6 more patients will be treated at the previous lower dose level.

Recruitment would be conducted until 6 patients are treated at one dose level without observed DLT. If no DLT occured in 6 patients, then this dose level would be used for phase II.
The safety DLTs were defined as toxicities attributable to vosaroxin, expected or unexpected, except if these were likely associated with another cause (example: cytopenias known to occur after chemotherapy, bleeding in the setting of thrombocytopenia).
The following was considered to be DLTs:

Hematologic toxicities:

- Prolonged neutropenia or thrombocytopenia of CTC ≥4° beyond day 35 not attributable to persistent leukemia

Non-hematologic toxicities:

- **Any 3° or 4° toxicity was considered a DLT EXCEPT:**
- 3° weight gain or loss
- 3° diarrhea despite optimal anti-diarrheal therapy

- 3° or 4° electrolyte abnormalities that resolve to ≤2° within 7 days with or without clinical intervention
- 3° or 4° nausea and vomiting
- 3° AST or ALT lasting ≤7 days
- 3° or 4° serum lipase that returns to baseline within 7 days of interrupting study drug
- 3° or 4° elevation of serum lipase without clinical signs or symptoms of pancreatitis
- 3° febrile neutropenia
- 3° infection with concurrent neutropenia 3° or 4°

Phase II part of the trial:

The primary endpoint of the phase II part of the study was CR/CRi rate. Simon's optimal two stage design was planned to be used to evaluate the activity of the combined treatment with vosaroxin and azacitidine in older (≥60 years) patients with newly diagnosed AML or MDS-EB-2, who are unlikely to benefit from standard intensive chemotherapy. The null hypothesis H_0: CR/CRi rate ≤ 30% for the overall population was planned to be tested at a one-sided significance level of 2.5%.
Secondary endpoints were CR_{MRD-}, DOR, EFS and OS, which were planned to be analyzed in an exploratory manner only by using uni- and multivariable methods such as logistic regression for binary outcome variables and Cox regression models for time-to-event outcomes.
The endpoint "quality of life" was planned to be assessed by self-administered questionnaires, including the EORTC Quality of Life Core Questionnaire (QLQ-C30). The questionnaire data was planned to be analyzed according to the strategy used by Messerer et al. and appropriated methods for ordinal data.
The amount of missing explanatory and response data was documented, including the proportion of missing values for each variable being analyzed. The characteristics of patients having missing variables was planned to be described. In general, it is not appropriate to exclude subjects having incomplete data from the analysis. Therefore, missing value imputation was planned to be used in general.

Since the trial was terminated prematurely after enrollment of 9 patients within the safety run-in phase, no analysis of the study endpoints could be performed.

20. Summary – Conclusions: Efficacy Results, Safety Results, Conclusion

20.1 Efficacy Results

Nine patients were enrolled within the safety run-in part of the trial.

Overall, 8 (89%) patients in the study cohort were male and 1 (11%) female. The median age was 71.4 years (range, 65 to 81 years). All patients were Caucasians. In 89 % of patients, ECOG performance status at baseline was reported “0”, one patient (11%) had an ECOG of “2”. The patients had a median Cumulative Illness Rating Score (CIRS) at study entry of 2 points (range, 1 to 11 points). Most of the patients (89%) had diagnosis of AML, one patient had MDS EB-2. Six (75%) of the AML patients had a secondary AML after MDS/MPN, two patients (25%) had a *de novo* AML.

One (11%) patient had a *FLT3*-ITD, but all patients were *NPM1* wildtype, *CEBPA* wildtype and *FLT3*-TKD negative. Only four patients had non-missing molecular assessments regarding ASXL1, RUNX1, and TP53. Among these four, three (75%) patients had an *ASXL1* mutation, 3 (75%) had a *RUNX1* mutation, but no patient had a *TP53* mutation.

Among the eight AML patients seven (88%) had an adverse risk classification according to ELN 2017 recommendations, one patient had an intermediate risk.

Baseline and disease characteristics are summarized in Appendix E.

None of the nine patients completed the study according to protocol. All patients withdrew prematurely. The main reasons were relapse (n=1) or progressive disease (n=2) and patient’s decision (n=3). Other reasons were death (n=1), allogeneic stem cell transplantation (n=1) and physician’s decision (n=1). No patient withdrew directly due to adverse events. Most patients discontinued the trial after treatment cycle 1 (n=4) and cycle 2 (n=2). Only two patients started with single azacitidine maintenance therapy, one patient directly after cycle 1 and another patient after cycle 5. One patient received 4 cycles of maintenance therapy and withdrew from study due to progressive disease. The other patient decided to discontinue treatment after 8 months of maintenance. Disposition of patients is displayed in Appendix D.

During study treatment, one patient (11%) achieved a complete remission (CR), 3 (33%) patients a complete remission with incomplete hematologic recovery (CRi) and one patient (11%) a partial remission (PR) as best response. Three (33%) patients had a stable disease (SD) and one patient had progressive disease. One of the four patients with CR/CRi had an early relapse after initial CRi.

Primary and secondary efficacy variables were not analyzed due to premature discontinuation of the trial after enrolment of 9 patients in the safety run-in phase. Quality of life also was not analyzed due to insufficient quantity of data.

20.2 Safety Results

Overall, nine patients were enrolled within the safety run-in phase of the trial.

Overall, three DLTs occurred in nine patients. Within the first three patients who were treated within the initial dose level “0” (70mg/m^2), one DLT (febrile neutropenia grade 4) occurred, therefore three additional patients were planned to be treated within this dose level. The second patient of this additional cohort developed prolonged neutropenia and thrombocytopenia of CTC ≥4° beyond day 35 not attributable to persistent leukemia, which was judged as DLT. Therefore, the next three patients were treated with the next lower vosaroxin dose of 50mg/m^2. In the third patient of this cohort DLTs (prolonged thrombocytopenia and febrile neutropenia) were reported and three more patients were scheduled for treatment at this dose level. One more patient was included before the trial was terminated prematurely. In this patient, no DLT occurred.

Overall, during the whole treatment period, AEs occurred most frequently in the categories of blood and bone marrow disorders (100%), investigations (100%), gastrointestinal disorders (78%), metabolism and nutrition disorders (78%) and general disorders and administration site conditions (67%).

The most frequently reported adverse events during study treatment were anemia and decreased platelet count (100%). Other adverse events occurring in more than 50% of patients were white blood cell count decreased (89%), neutrophil count decreased (78%), hypokalemia (78%), constipation (78%), edema limbs (67%), oral mucositis (56%) and fatigue (56%).

During single azacitidine maintenance therapy, anemia, injection site reactions, white blood count decreased and insomnia were reported as adverse events in both patients receiving maintenance. A summary of AEs is displayed in Appendix F.

Over the whole treatment period, the frequently occurring severe adverse reactions (>50%) with CTCAE grade ≥3 included platelet count decreased (100%), anemia (89%), white blood cell count decreased (89%), neutrophil count decreased (78%) and hypokalemia (56%).

A total of 11 serious adverse events (SAEs) were reported in 4 (44%) patients of which 10 SAEs (91%) were treatment-related. Most of the SAEs (73%) occurred during the first two treatment cycles. A listing of reported SAEs is displayed in Appendix G.

The most frequent SAEs which were reported during study treatment were infections (n=3 sepsis, n=1 urinary tract infection) and pyrexia (n=2). Other SAEs reported were febrile neutropenia, bifascicular block, stomatitis, hepatic enzyme increased and altered state of consciousness. Two SAEs were assessed to be a Suspected unexpected serious adverse reaction (SUSAR) by the sponsor: Septic shock and impaired consciousness, which occurred both within the same patient. One SAE (septic shock) had a fatal outcome.

Overall, n=5 patients died. One patient died during study treatment after cycle 2 due to septic shock. Four other patients died during follow-up. N=4 patients were alive at the end of trial. 30-day mortality was 0%, 60-day mortality was 11.1% (1/9).

There were no cases of premature discontinuation from the study treatment due to adverse events.

20.3 Conclusion

Discussion and overall conclusion

On October 31st 2019 the study was early terminated, since the manufacturer of vosaroxin, SUNESIS Pharmaceuticals, Inc., had discontinued the development program of the investigational drug vosaroxin. It was not possible to continue the trial beyond the safety run-in phase since the label of the investigational drug expired latest at the end of 2019 and could not be renewed.

Therefore primary and secondary efficacy variables were not analyzed due to premature termination of the trial.

The study population consisted of older patients with newly diagnosed AML and intermediate or adverse genetic risk or MDS-EB-2 who generally have a poor pognosis. Seven AML patients were adverse risk according to ELN 2017 recommendations, one patient had an intermediate risk. Looking at response rates in a descriptive manner, four patients achieved a CR/CRi and 1 patient a PR as best response. There were three patients with a SD and one patient had a progressive disease.

Also, the safety run-in phase was not completed according to protocol. The last administered dose level was 50mg/m^2 (level "-1"), but maximal tolerated dose (MTD) could not be defined finally, since at least one more patient would have to be treated within the safety run-in part to make a conclusion regarding the MTD.

Overall, there were 11 SAE in this trial; among these, one SAE had a fatal outcome. Taken together, frequency of toxicities and deaths were comparable to that observed in other studies in older patients with AML.

21. Date of Report

Date 26.10.2020

V. Gaidzik

PD Dr. Verena Gaidzik
Co-ordinating Investigator

Appendix A
Response criteria in acute myeloid leukemia:

Adapted from Döhner H, Estey E, Grimwade D, et al. Diagnosis and Management of Acute Myeloid Leukemia in Adults: 2017 Recommendations from an International Expert Panel, on Behalf of the European LeukemiaNet. Blood. 2016 Nov 28.

Table 6. Response criteria in acute myeloid leukemia

Category	Definition	Comment
Response		
• CR without minimal residual disease (CR_{MRD-})	If studied pre-treatment, CR with negativity for a genetic marker by real-time quantitative polymerase chain reaction (RT-qPCR), or CR with negativity by multi-color flow cytometry	Sensitivities vary by marker tested, and by method used; therefore, test used and sensitivity of the assay should be reported; analyses should be done in experienced laboratories (centralized diagnostics)
• Complete remission (CR)	Bone marrow blasts <5%; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count $\geq$1.0 x 10^9/L (1,000/μL); platelet count $\geq$100 x 10^9/L (100,000/μL)	MRD positive or unknown
• CR with incomplete hematologic recovery (CR_i)	All CR criteria except for residual neutropenia [<1.0 x 10^9/L (1,000/μL)] or thrombocytopenia [<100 x 10^9/L (100,000/μL)]	
• Morphologic leukemia-free state (MLFS)	Bone marrow blasts <5%; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required	Marrow should not merely be "aplastic"; at least 200 cells should be enumerated or cellularity should be at least 10%
• Partial remission (PR)	All hematologic criteria of CR; decrease of bone marrow blast percentage to 5% to 25%; and decrease of pretreatment bone marrow blast percentage by at least 50%	Especially important in the context of phase 1-2 clinical trials

Appendix B
Response criteria in myelodysplasia:

Adapted from Bruce D. Cheson, Peter L. Greenberg, John M. Bennett, Bob Lowenberg, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood.2006;108:419-425.

Table 3. Proposed modified International Working Group response criteria for altering natural history of MDS[7]

Category	Response criteria (responses must last at least 4 wk)
Complete remission	Bone marrow: ≤ 5% myeloblasts with normal maturation of all cell lines*
	Persistent dysplasia will be noted*†
	Peripheral blood‡
	Hgb ≥ 11 g/dL
	Platelets ≥ 100×10^9/L
	Neutrophils ≥ 1.0×10^9/L†
	Blasts 0%
Partial remission	All CR criteria if abnormal before treatment except:
	Bone marrow blasts decreased by ≥ 50% over pretreatment but still > 5%
	Cellularity and morphology not relevant
Marrow CR†	Bone marrow: ≤ 5% myeloblasts and decrease by ≥ 50% over pretreatment†
	Peripheral blood: if HI responses, they will be noted in addition to marrow CR†
Stable disease	Failure to achieve at least PR, but no evidence of progression for > 8 wks
Failure	Death during treatment or disease progression characterized by worsening of cytopenias, increase in percentage of bone marrow blasts, or progression to a more advanced MDS FAB subtype than pretreatment
Relapse after CR or PR	At least 1 of the following:
	Return to pretreatment bone marrow blast percentage
	Decrement of ≥ 50% from maximum remission/response levels in granulocytes or platelets
	Reduction in Hgb concentration by ≥ 1.5 g/dL or transfusion dependence
Cytogenetic response	Complete
	Disappearance of the chromosomal abnormality without appearance of new ones
	Partial
	At least 50% reduction of the chromosomal abnormality
Disease progression	For patients with:
	Less than 5% blasts: ≥ 50% increase in blasts to > 5% blasts
	5%-10% blasts: ≥ 50% increase to > 10% blasts
	10%-20% blasts: ≥ 50% increase to > 20% blasts
	20%-30% blasts: ≥ 50% increase to > 30% blasts
	Any of the following:
	At least 50% decrement from maximum remission/response in granulocytes or platelets
	Reduction in Hgb by ≥ 2 g/dL
	Transfusion dependence
Survival	Endpoints:
	Overall: death from any cause
	Event free: failure or death from any cause
	PFS: disease progression or death from MDS
	DFS: time to relapse
	Cause-specific death: death related to MDS

Deletions to IWG response criteria are not shown.

To convert hemoglobin from grams per deciliter to grams per liter, multiply grams per deciliter by 10.

MDS indicates myelodysplastic syndromes; Hgb, hemoglobin; CR, complete remission; HI, hematologic improvement; PR, partial remission; FAB, French-American-British; AML, acute myeloid leukemia; PFS, progression-free survival; DFS, disease-free survival.

*Dysplastic changes should consider the normal range of dysplastic changes (modification).[41]

†Modification to IWG response criteria.

‡In some circumstances, protocol therapy may require the initiation of further treatment (eg, consolidation, maintenance) before the 4-week period. Such patients can be included in the response category into which they fit at the time the therapy is started. Transient cytopenias during repeated chemotherapy courses should not be considered as interrupting durability of response, as long as they recover to the improved counts of the previous course.

Appendix C
Background information and study rationale

Introduction

Acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) are genetically and clinically heterogeneous disorders and outcomes are influenced by various factors, including patient features [e.g., age, comorbidities, performance status (PS)] and disease characteristics (e.g., genetics of leukemic cells) [1-3]. Combination of an anthracycline with cytarabine ('3+7') remains the standard of care for intensive induction therapy in AML patients considered medically fit and results in complete remission (CR) rates in the range of 65%-75% in younger (≤60 years) and of 40%-60% in older (>60 years) adult patients. While the value of post-remission therapy in older AML continues to be a matter of debate, the choice of consolidation in younger patients is guided by cytogenetic and molecular genetic features and can range from higher doses of cytarabine to allogeneic hematopoietic cell transplantation (HCT). Following intensive treatment, the overall survival (OS) at 5 years in younger patients is in the range of 40%-45%; in older patients OS still remains poor with less than 10% being alive after 5 years [4]. It has been shown that patients with high-risk MDS classified as refractory anemia with excess blasts-2 (RAEB-2) [in World Health Organization (WHO) 2016 classification now designated as MDS with excess blasts-2 (MDS-EB-2)] have outcomes similar to patients with AML [5] and therefore are included in this clinical study.

Vosaroxin is a first-in-class anticancer quinolone derivative, which inhibits topoisomerase-II enzymes and intercalates DNA causing site-specific DNA double strand breaks. It evades p-glycoprotein mediated cellular extrusion and can induce apoptosis independent of p53. It is associated with limited reactive oxygen species formation leading to reduced potential for cardiotoxicity [6-11]. In a phase I/II study in relapsed/refractory AML, good tolerability and promising efficacy have been shown in combination with a cytarabine chemotherapy backbone [12-13]. In a recently reported large randomized international trial (VALOR-study, NCT01191801) in relapsed/refractory AML evaluating in a double blinded manner intermediate-dose cytarabine with or without vosaroxin, clinical significant efficacy in terms of CR rates, event-free survival (EFS) and OS has been shown especially in patients >60 years and in those with an early relapse (within one year) [15]. In addition, in a single arm phase-II study (NCT01893320) in patients not fit for intensive chemotherapy the combination of vosaroxin with decitabine showed promising results and a favorable safety profile. These encouraging results provide a rationale to extend the use of vosaroxin to patients with newly diagnosed AML and especially to the subset with an urgent medical need, that are older patients above the age of 60 years with intermediate and adverse genetic risk who are unlikely to benefit from standard intensive chemotherapy.

Vosaroxin

a) Pre-clinical pharmacology

Vosaroxin is a first-in-class anticancer quinolone derivative that intercalates DNA and inhibits topoisomerase II. Vosaroxin induces replication-dependent, site-selective double-strand DNA breaks, S-phase lag, and G2/M arrest, leading to apoptosis [6-7,9-10].

Vosaroxin antineoplastic activity appears to be exclusively mediated through DNA intercalation and topoisomerase II inhibition. In comparison to approved topoisomerase II inhibitors, vosaroxin is minimally metabolized, and significant free radical formation, reactive oxygen species (ROS), toxic metabolites, DNA crosslinks, or DNA alkylation are not associated with its stable core quinolone structure [6].

Vosaroxin demonstrated broad cytotoxic activity against cancer cell lines, patient biopsies and in mouse models. In combination with a number of anticancer agents, vosaroxin had additive or synergistic activity. Vosaroxin combined with cytarabine was synergistic in AML patient samples, and the combination showed enhanced activity in a normal mouse bone marrow (BM) ablation model [6,11].

Vosaroxin is not a substrate of P-glycoprotein and can induce apoptosis independent of p53. Vosaroxin was active in models of cancer drug resistance in vitro and in vivo [7].

b) Pre-clinical safety

A series of safety pharmacology/secondary pharmacodynamic studies was conducted to assess the effects of vosaroxin on cardiovascular, respiratory, gastrointestinal (GI), renal, and nervous system function. Effects on cardiovascular function in the dog were limited to transient hypotension and slight transient reduction in femoral blood flow, and seen only at the highest dose level (200 mg/m^2). Gastric emptying and/or gastric volume were reduced, and gastric pH was increased in rats at doses ≥3 mg/kg (≥18 mg/m^2). The cardiovascular and GI effects observed in dogs and rats were somewhat consistent with effects noted at relatively high concentrations in studies performed *in vitro* with guinea pig heart, rabbit heart, and GI tissue. Vosaroxin had no clinically relevant effect on coagulation or platelet aggregation. Vosaroxin did not inhibit hERG channels in vitro. In renal function studies in rat, no clearly consistent or dose-responsive effects on urine volume or electrolyte (sodium, chloride, potassium) excretion were noted at doses up to 50 mg/kg (300 mg/m^2). There were no effects of single IV doses of vosaroxin up to 50 mg/kg (150 mg/m^2) in mice in a series of assays designed to assess effects on overall behaviour, locomotor activity, and reactivity to selected types of noxious stimuli (hot plate, electroshock, acetic acid). Vosaroxin had no local anaesthetic effects when applied to the eyes of guinea pigs at concentrations up to 100 µg/mL [7].

c) Clinical experience

Vosaroxin has demonstrated clinical activity in four completed Sunesis-sponsored studies in patients with hematologic malignancies. Three of these studies were early-phase trials: SPO-0004 (advanced hematologic malignancies); SPO-0012 (relapsed or refractory AML); and SPO-0014 (previously untreated AML patients ≥60 years of age). One study was a phase 3, randomized, double-blind, controlled, study of vosaroxin and cytarabine *versus* (*vs*) placebo and cytarabine in first relapsed or refractory AML (VALOR) [15]. The VALOR study demonstrated an OS benefit in favor of vosaroxin and cytarabine. Although the primary OS analysis using unstratified log rank test was not significant, the stratified test and OS analysis with censoring for transplantation demonstrated significant improvements in survival (n=711; Hazard ratio HR= 0.87). Also, the OS benefit data are supported by a robust effect on CR with doubling of the CR rate (30.1% *vs* 16.3%, 2-sided p<0.0001) in favor of the vosaroxin-arm compared to the control-arm. For patients ≥60 years of age, both unstratified and stratified OS analysis showed significant improvements (n=451; HR= 0.76, 1-sided p=0.0015).

Vosaroxin has also been studied in five non-Sunesis-sponsored studies. LI-1 was an investigator initiated trial (IIT) conducted at Cardiff University, Cardiff UK, in older patients (≥60 years of age) with primary or secondary AML and high-risk MDS. Patients enrolled were chemotherapy-naïve and considered ineligible for standard intensive chemotherapy due to age and fitness status. The study included two vosaroxin arms. The first arm investigated vosaroxin alone *vs* low dose cytarabine (LDAC) alone; the second investigated vosaroxin in combination with LDAC *vs* LDAC alone. All investigational arms were discontinued because the pre-specified remission rate criteria for advancement to phase 3 based on the pick a winner design were not achieved [16].

Another IIT is performed at the MD Anderson Cancer Center; in this phase I/II study, vosaroxin is combined with decitabine in older patients with AML and high-risk MDS. The results of this ongoing study show high response rates and a low treatment-related mortality particularly for the lower vosaroxin dose level of 70 mg/m^2 compared to 90 mg/m^2. Among all 56 patients evaluable for response, 30 (54%) achieved CR, 8 (14%) CR with incomplete platelet recovery (CRp), and 5 (9%) CR with incomplete blood count recovery (CRi) resulting in an overall response rate (ORR) of 77%; 4-week and 8-week mortality for all patients were 0% and 14%, respectively. The regimen was generally well tolerated with the main ≥3° toxicities being mucositis in 10 (18%) and liver enzyme elevation in 8 (14%) patients [17].

Two IITs investigating safety and clinical activity of vosaroxin as a single agent and in combination with azacitidine in patients with MDS are ongoing. The interim results of the second study “Phase I study of vosaroxin plus azacitidine for patients with myelodysplastic syndrome” were presented at the American Society of Hematology (ASH) congress in December 2015. Twelve patients completed at least one cycle in the dose escalation cohort were evaluable for response. Best response for each patient was as follows: stable disease (SD), n=3; SD with hematologic improvement (HI)-

neutrophils, n=1; CR, n=3; CRi, n=5. Of these twelve patients, five (42%) have proceeded on to HCT [18].

Vosaroxin has shown limited clinical activity as a single agent in three completed phase 2 Sunesis-sponsored studies in patients with advanced solid tumors: SPO-0005 (Second-Line Chemotherapy in Patients With Advanced Non-Small Cell Lung Cancer), SPO-0006 (Second-Line Chemotherapy in Patients With Advanced Non-Small Cell Lung Cancer), and SPO-0010 (Platinum-resistant ovarian cancer, primary peritoneal carcinoma, or fallopian tube cancer).

Summary of Key Safety Information for Study Drugs

a) Vosaroxin

As of the data cut-off in 15 Nov 2014, cumulative safety data for vosaroxin are available for 1282 patients in 10 Sunesis-sponsored studies. This includes 648 patients treated with vosaroxin alone or in combination with cytarabine with hematologic malignancies (including the VALOR study) and 284 vosaroxin-treated patients with advanced solid tumors. In addition, safety data are presented for 168 patients in five non-Sunesis sponsored studies with hematologic malignancies, including LI-1, who were treated with vosaroxin alone or in combination with another chemotherapeutic agent [6].

Of the 932 patients with hematologic malignancies and advanced solid tumors who received vosaroxin alone or in combination with cytarabine, 94.7% reported at least one adverse drug reaction (ADR): 95.5% of 648 patients with hematologic malignancies and 93.0% of 284 patients with advanced solid tumors. Overall and regardless of indication, the most frequently reported ADR was nausea. ADRs in the GI Disorders System Organ Class (SOC) were more commonly reported as 1° and 2°, while ADRs in the Blood and Lymphatic System SOC were more commonly reported as 3° and 4°. These observations are consistent with previous findings and expected in these patient populations.

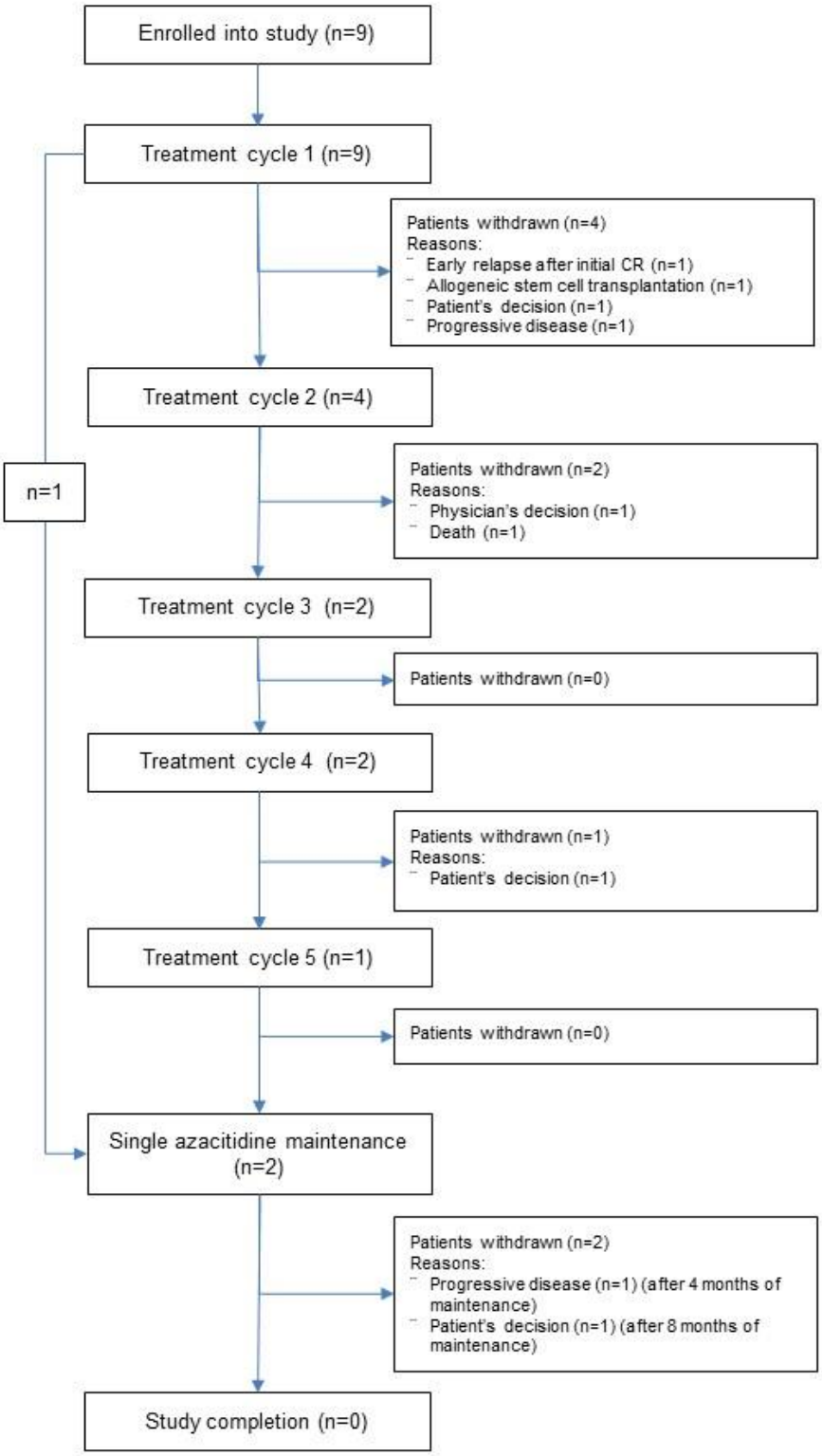
The safety profile of vosaroxin is consistent with past clinical findings, non-clinical toxicology, and the documented common pharmacologic effects of other cytotoxic chemotherapeutic agents. Myelosuppression (including associated infections) and GI toxicity (such as upper GI mucositis, nausea, vomiting) are the most frequently reported AEs and are expected with vosaroxin. Unblinded VALOR data revealed an increased incidence of fatal infections in the patients who received vosaroxin in combination with cytarabine as compared with patients who received cytarabine and placebo. However, all-cause 30- and 60-day mortality was comparable between the two treatment arms. Thirty-day mortality in the experimental (vosaroxin/cytarabine) arm and standard (vosaroxin/placebo) arm was 7.9% and 6.6%, respectively; 60-day mortality in the vosaroxin/cytarabine arm and vosaroxin/placebo arm was 19.7% and 19.4%, respectively. For patients ≥60 years of age, all-cause mortality was comparable in between the vosaroxin/cytarabine and vosaroxin/placebo arm (10.2% vs. 9.0% at 30 days, and 20.4% vs. 22.6% at 60 days). Based on multivariate analysis, the treatment in the vosaroxin/cytarabine arm was not predictive for increased 30-day or

60-day mortality. Eastern Cooperative Oncology Group (ECOG) >1 was predictive (p< 0.05) of 30-day mortality (Odds ratio [OR]=3.2) and 60-day mortality (OR=2.1). Additional predictive factors identified for 30-day mortality were hemoglobin <10 g/dL (OR=3.8) and bilirubin >1.0 mg/dL (OR=3.3). For 60-day mortality, other predictive factors were albumin ≤3.6 g/dL (OR=2.0), BM blasts 10% to <30% [OR=2.6] or ≥30% [OR=6.3]), prior history of MDS (OR=2.2), and achievement of CR/CRi with first-line therapy (OR=0.66). Age (<65 years *vs* 65-69 years *vs* 70-74 years *vs* ≥75 years) was not a significant predictor of early mortality in the vosaroxin/cytarabine arm in the univariate logistic regression and therefore was not selected for multivariate analysis. Interestingly, age was predictive of 30-day mortality in the vosaroxin/placebo arm. When added to the final multivariate model, age was of borderline significance (p=0.06) [19].
The potential risks associated with vosaroxin treatment are manageable, and do not outweigh the potential clinical benefit given the unmet need in terms of treatment for older patients with AML or high-risk MDS, who still have a very dismal outcome following current treatment.

b) Azacitidine

Azacitidine is approved in Europe for the treatment of adult patients with intermediate-2 and high-risk MDS as well AML who are not eligible for allogeneic HCT.
The most commonly reported adverse reactions with azacitidine treatment were haematologic reactions (71.4 %) including thrombocytopenia, leukocytopenia and neutropenia (commonly 3°-4°), GI events (60.6 %) including nausea, vomiting (commonly 1°-2°) or injection site reactions (77.1 %; commonly 1°-2°).
For further information please refer to the Summary of product characteristics.

Appendix D
Patient disposition



Appendix E
Patient baseline and disease characteristics

Demographics and baseline characteristics		
Variable	**Category**	**n (%)**
Sex	Male Female	8 (89) 1 (11)
Ethnicity	Caucasian Asian North African / Arabian / Turk Other African Other	9 (100) 0 0 0 0
WHO/ECOG performance status	0 1 2 3 4	8 (89) 0 1 (11) 0 0
Initial diagnosis	AML MDS RAEB-2	8 (89) 1 (11)
If AML, type of AML	*De novo* AML Secondary AML after MDS/MPS Treatment-related AML Missing	2 (25) 6 (75) 0 0
ELN 2017 classification (AML)	Favorable Intermediate Adverse	0 1 (13) 7 (87)
	Unit	**Median (Range)**
Age	Years	71.4 (65.8 – 81.8)
CIRS score	Points	2 (1 -11)
LDH	U/l	219 (119 - 620)
Hemoglobin	g/dl	9.2 (7.5 - 13.2)
Platelets	G/l	77 (12 - 437)
White blood count	G/l	2.5 (0.5 – 52.8)
BM blasts	%	25 (9 – 50)
PB blasts	%	0 (0 – 10)
Molecular genetics		
***FLT3*-ITD**	Negative *FLT3*-ITD low *FLT3*-ITD high	8 (89) 1 (11) 0
***FLT3*-TKD**	Negative Positive	9 (100) 0
NPM1	Wildtype Mutation	9 (100) 0
CEBPA	Wildtype Monoallelic mutation	9 (100) 0

	Biallelic mutation	
ASXL1	Wildtype Mutation Missing	1 (25) 3 (75) 5
RUNX1	Wildtype Mutation Missing	1 (25) 3 (75) 5
TP53	Wildtype Mutation Missing	4 (100) 0 5

Appendix F
Incidence of adverse events by CTCAE Short Name, relatedness to study drugs and CTCAE grade (overall treatment period)

CTCAE Category	CTCAE Short Name				
Number of patients		**N=9**			
		n (%)	**n (%) related to study drugs**	**n (%) < CTCAE grade 3**	**n (%) ≥ CTCAE grade 3**
Blood and lymphatic system disorders	Anemia	9 (100)	8 (89)	1 (11)	8 (89)
	Blood and lymphatic system disorders - Other	1 (11)	1 (11)	1 (11)	0
	Febrile neutropenia	4 (44)	4 (44)	0	4 (44)
	Leukocytosis	1 (11)	0	0	1 (11)
	Lymph node pain	1 (11)	0	1 (11)	0
	Thrombotic thrombocytopenic purpura	1 (11)	0	1 (11)	0
Cardiac disorders	Atrial fibrillation	2 (22)	2 (22)	1 (11)	1 (11)
	Cardiac disorders - Other	1 (11)	0	1 (11)	0
	Ventricular arrhythmia	1 (11)	0	1 (11)	0
Ear and labyrinth disorders	Ear pain	1 (11)	0	0	1 (11)
Eye disorder	Dry eye	1 (11)	1 (11)	1 (11)	0
	Scleral disorder	1 (11)	1 (11)	1 (11)	0
Gastrointestinal disorders	Constipation	7 (78)	3 (33)	7 (78)	0
	Diarrhea	3 (33)	3 (33)	3 (33)	0

	Dry mouth	1 (11)	1 (11)	1 (11)	0
	Dyspepsia	3 (33)	3 (33)	3 (33)	0
	Mucositis oral	5 (56)	5 (56)	3 (33)	2 (22)
	Nausea	4 (44)	4 (44)	4 (44)	0
	Oral hemorrhage	3 (33)	2 (22)	3 (33)	0
	Periodontal disease	1 (11)	0	1 (11)	0
	Stomach pain	1 (11)	1 (11)	1 (11)	0
	Vomiting	4 (44)	3 (33)	4 (44)	0
General disorders and administration site conditions	Chills	2 (22)	2 (22)	2 (22)	0
	Edema limbs	6 (67)	2 (22)	4 (44)	2 (22)
	Fatigue	5 (56)	5 (56)	4 (44)	1 (11)
	Fever	4 (44)	4 (44)	4 (44)	0
	Injection site reaction	3 (33)	3 (33)	3 (33)	0
	Non-cardiac chest pain	1 (11)	1 (11)	1 (11)	0
	Pain	1 (11)	0	1 (11)	0
Hepatobiliary disorders	Hepatobiliary disorders - Other	1 (11)	1 (11)	0	1 (11)
Infections and infestations	Enterocolitis infectious	1 (11)	1 (11)	0	1 (11)
	Infections and infestations - Other	3 (33)	0	0	3 (33)
	Lip infection	1 (11)	1 (11)	1 (11)	0
	Mucosal infection	1 (11)	1 (11)	1 (11)	0
	Pharyngitis	1 (11)	0	1 (11)	0
	Sepsis	4 (44)	4 (44)	0	4 (44)

	Sinusitis	1 (11)	1 (11)	1 (11)	0
	Skin infection	1 (11)	1 (11)	1 (11)	0
	Tooth infection	1 (11)	1 (11)	0	1 (11)
Investigations	Creatinine increased	1 (11)	1 (11)	1 (11)	0
	Electrocardiogram QT corrected interval prolonged	2 (22)	2 (22)	2 (22)	0
	Investigations - Other (LDH increase)	1 (11)	1 (11)	1 (11)	0
	Lymphocyte count decreased	1 (11)	1 (11)	0	1 (11)
	Neutrophil count decreased	7 (78)	7 (78)	0	7 (78)
	Platelet count decreased	9 (100)	8 (89)	0	9 (100)
	Weight gain	1 (11)	0	1 (11)	0
	White blood cell decreased	8 (89)	7 (78)	0	8 (89)
Metabolism and nutrition disorders	Anorexia	4 (44)	2 (22)	4 (44)	0
	Hypoalbuminemia	2 (22)	1 (11)	2 (22)	0
	Hypocalcemia	1 (11)	1 (11)	1 (11)	0
	Hypokalemia	7 (78)	2 (22)	2 (22)	5 (56)
Musculoskeletal and connective tissue disorders	Arthritis	1 (11)	0	1 (11)	0
	Back pain	1 (11)	0	1 (11)	0
	Chest wall pain	1 (11)	1 (11)	1 (11)	0
	Neck pain	1 (11)	0	0	1 (11)
	Pain in extremity	1 (11)	1 (11)	1 (11)	0
Nervous system disorders	Depressed level of consciousness	1 (11)	1 (11)	0	1 (11)

	Headache	2 (22)	0	2 (22)	0
	Syncope	1 (11)	0	0	1 (11)
Psychiatric disorders	Agitation	1 (11)	1 (11)	0	1 (11)
	Depression	1 (11)	0	1 (11)	0
	Insomnia	3 (33)	0	3 (33)	0
	Restlessness	1 (11)	0	1 (11)	0
Renal and urinary disorders	Renal and urinary disorders - Other (Fluid retention, edema)	1 (11)	1 (11)	1 (11)	0
	Urinary incontinence	1 (11)	1 (11)	1 (11)	0
Reproductive system and breast disorders	Prostatic obstruction	1 (11)	0	1 (11)	0
Respiratory, thoracic and mediastinal disorders	Dyspnea	1 (11)	1 (11)	1 (11)	0
	Epistaxis	2 (22)	2 (22)	2 (22)	0
	Hiccups	1 (11)	1 (11)	1 (11)	0
	Hypoxia	1 (11)	1 (11)	0	1 (11)
	Pneumonitis	1 (11)	1 (11)	1 (11)	0
Skin and subcutaneous tissue disorders	Pruritus	2 (22)	2 (22)	2 (22)	0
	Rash acneiform	1 (11)	1 (11)	1 (11)	0
	Rash maculo-papular	3 (33)	2 (22)	3 (33)	0
	Skin and subcutaneous tissue disorders - Other	2 (22)	2 (22)	2 (22)	0
	Skin ulceration	1 (11)	1 (11)	1 (11)	0
Vascular disorders	Hematoma	2 (22)	1 (11)	2 (22)	0
	Hypertension	3 (33)	1 (11)	0	3 (33)

	Hypotension	1 (11)	1 (11)	0	1 (11)
	Superficial thrombophlebitis	1 (11)	0	1 (11)	0

Appendix G
List of Serious Adverse Events

Patient number	Age (y)	Sex	Serious adverse event term (Verbatim)	Dates		Severity (CTCAE grade)	Relationship to study treatment	Outcome
				Start	Stop			
513051	65	male	Sepsis	18-Okt-18	13-Nov-18	4	related	recovered
580294	81	female	Fever	05-Mai-19	10-Mai-19	1	related	recovered
580294	81	female	Fever	12-Mai-19	20-Mai-19	2	related	recovered
580294	81	female	Urinary tract infection	21-Aug-19	04-Sep-19	2	related	recovered
753813	74	male	Fever in neutropenia	23-Jul-18	31-Jul-18	3	related	not recovered
753813	74	male	Mucositis	23-Jul-18	31-Jul-18	3	related	not recovered
753813	74	male	Septic shock	27-Jul-18	31-Jul-18	5	related	fatal
753813	74	male	Impaired consciousness	27-Jul-18	31-Jul-18	4	related	not recovered
981075	78	male	Sepsis (gram-negative)	29-Jun-18	25-Jul-18	4	related	recovered
981075	78	male	Hepatic enzymes increased	23-Jul-18	22-Aug-18	3	not related	recovered
981075	78	male	Cardiac disorders (Bifascicular block)	15-Mai-19	26-Jun-19	1	related	recovered with se-queleae

Appendix H
References

1. Burnett AK, Milligan D, Prentice AG, et al. Comparison of low-dose cytarabine and hydroxyurea with or without all-trans retinoic acid for acute myeloid leukemia and high-risk myelodysplastic syndrome in patients not considered fit for intensive treatment. Cancer 2007;109:1114-24.
2. Tsurumi H, Kanemura N, Hara T, et al. Therapeutic strategy of untreated de novo acute myeloid leukemia in the elderly: the efficacy of continuous drip infusion with low dose cytarabine and etoposide. J Cancer Res Clin Oncol. 2007;133:547-553.
3. Kanemura N, Tsurumi H, Kasahara S, et al. Continuous drip infusion of low dose cytarabine and etoposide with granulocyte colony-stimulating factor for elderly patients with acute myeloid leukaemia ineligible for intensive chemotherapy. Hematol Oncol. 2008;26:33-38.
4. Hütter ML, Döhner K, Schmidt-Wolf I, et al. Role of etoposide in combination with all-trans retinoic acid in the treatment of elderly patients with acute myeloid leukemia and *NPM1* mutation. Blood. 2008;112:559 (abstract).
5. Farag SS, Ruppert AS, Mrózek K, et al. Outcome of induction and postremission therapy in younger adults with acute myeloid leukemia with normal karyotype: a cancer and leukemia group B study. J Clin Oncol. 2005;23:482-493.
6. Schlenk RF, Fröhling S, Hartmann F, et al. Intensive consolidation versus oral maintenance therapy in patients 61 years or older with acute myeloid leukemia in first remission: results of second randomization of the AML HD98-B treatment trial. Leukemia. 2006;20:748-750.
7. Schlenk RF, Fröhling S, Hartmann F, Fischer JT, Glasmacher A, del Valle F, et al. Phase III study of all-trans retinoic acid in previously untreated patients 61 years or older with acute myeloid leukemia. Leukemia. 2004;18:1798-803.
8. Schlenk RF, Döhner K, Kneba M, et al. Gene Mutations and Response to Treatment with All-Trans Retinoic Acid in Elderly Patients with Acute Myeloid Leukemia – Results from AMLSG Trial AML HD98B. Haematologica. 2009;94:54-60.
9. Schlenk RF, Döhner K, Krauter J, et al. All-Trans Retinoic Acid Improves Outcome in Younger Adult Patients with Nucleophosmin-1 Mutated Acute Myeloid Leukemia – Results of the AMLSG 07-04 Randomized Treatment Trial. Blood (ASH Annual Meeting Abstracts), Nov 2011; 118: 80.
10. Schlenk RF, Lübbert M, Benner A, et al; German-Austrian Acute Myeloid Leukemia Study Group. All-trans retinoic acid as adjunct to intensive treatment in younger adult patients with acute myeloid leukemia: results of the randomized AMLSG 07-04 study. Ann Hematol. 2016;95(12):1931-1942

11. Sanz MA, Grimwade D, Tallman MS, Lowenberg B, Fenaux P, Estey EH, Naoe T, Lengfelder E, Buchner T, Dohner H, Burnett AK, Lo-Coco F. Guidelines on the management of acute promyelocytic leukemia: Recommendations from an expert panel on behalf of the European LeukemiaNet. Blood. 2009;113:1875-91.

12. Kanemura N, Tsurumi H, Kasahara S, et al. Continuous drip infusion of low dose cytarabine and etoposide with granulocyte colony-stimulating factor for elderly patients with acute myeloid leukaemia ineligible for intensive chemotherapy. Hematol Oncol. 2008;26:33-38.

13. Döhner H, Estey EH, Amadori S, Appelbaum FR, Büchner T, Burnett AK, Dombret H, Fenaux P, Grimwade D, Larson RA, Lo-Coco F, Naoe T, Niederwieser D, Ossenkoppele GJ, Sanz MA, Sierra J, Tallman MS, Löwenberg B, Bloomfield CD; European LeukemiaNet. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. Blood. 2010;115:453-74.

14. Messerer D, Engel J, Hasford J, Schaich M, Ehninger G, Sauerland C, Büchner T, Schumacher A, Krahl R, Niederwieser D, Krauter J, Ganser A, Creutzig U, Döhner H, Schlenk RF; German AML Intergroup. Impact of different post-remission strategies on quality of life in patients with acute myeloid leukemia. Haematologica. 2008;93:826-33.

15. Estey E, Döhner H. Acute myeloid leukaemia. Lancet. 2006;368:1894-907.

16. Arber DA, Vardiman JW, Brunning RD, et al. Acute myeloid leukaemia with recurrent genetic abnormalities. In: WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Fourth Edition. Edited by Swerdlow, S.H., Campo, E., Harris, N.L., Jaffe, E.S., Pileri, S.A., Stein, H., Thiele, J., Vardiman, J.W (editors). Geneva, Switzerland. WHO PRESS 2008

17. Grisendi S, Mecucci C, Falini B, et al. Nucleophosmin and cancer. Nat Rev. 2006;6:493-505.

18. Falini B, Mecucci C, Tiacci E, et al. Gimema Acute Leukemia Working Party. Cytoplasmic nucleophosmin in acute myelogenous leukemia with a normal karyotype. N Engl J Med. 2005;352:254-66.

19. Falini B, Nicoletti I, Martelli MF, et al. Acute myeloid leukemia carrying cytoplasmic/mutated nucleophosmin (NPMc AML): biological and clinical features. Blood. 2007;109:874-85.