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Protocol Page

A Phase I/II Study of Vosaroxin and Decitabine in Older Patients with Acute Myeloid Leukemia and High-risk Myelodysplastic Syndrome
2013-0099

Core Protocol Information

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Protocol Body

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A Phase 1/11 Study of Vosaroxin and Decitabine in Older Patients with Acute Myeloid Leukemia and High-risk Myelodysplastic Syndrome

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1.1 HYPOTHESIS AND OBJECTIVES:

1.2 Hypothesis:

Vosaroxin (formerly voreloxin), a DNA topoisomerase II inhibitor, and decitabine (Dacogen®; DAC) an analogue of the natural nucleoside 2'-deoxycytidine with hypomethylating activity, are effective and overall tolerable treatments for older patients with acute myeloid leukemia (AML) and high-risk myelodysplastic syndromes (MDS). Combination of these agents in older patients with AML and high-risk MDS may improve the overall clinical response to therapy without causing excessive toxicity. We propose an open label, phase IIII trial using vosaroxin in combination with decitabine in older patients with AML and high-risk MDS.

1.2 Objectives:

1.2.1 Primary:

Phase I:

- To detennine the safety ofvosaroxin in combination with decitabine in patients with high-risk MDS or AML who are elderly (age 60) and/or unable to tolerate standard therapy and to determine phase II schedule.

- To detennine the maximum tolerated dose (MTD) and dose limiting toxicity (DLT) of vosaroxin in combination with decitabine in patients with high-risk MDS or AML who are elderly (age 60) and/or unable to tolerate standard therapy.

Phase II:

- To determine the overall response rate (ORR) of vosaroxin in combination with decitabine in patients with high-risk MDS or AML who are elderly (age 60) and/or unable to tolerate standard therapy. Overall response rate = Complete response (CR) + CR without platelet recovery (CRp) + CR with insufficient hematological recovery (CRi).

1.2.2 Secondary :

Phase II:

- To detennine the safety ofvosaroxin in combination with decitabine in patients with high-risk Myelodysplastic Syndrome or Acute Myeloid Leukemia who are elderly (age 60) and/or unable to tolerate standard therapy.
- To determine the duration of response of patients with AML and high-risk MDS treated with this combination.
- To determine the disease-free survival (DFS) of patients with AML and high-risk MDS treated with this combination

- To determine the induction mortality (mortality within first 8 weeks of initiation of therapy) for patients with AML and high-risk MDS treated with this combination.
- To detennine the toxicity of the regimen for patients with AML and high-risk MDS treated with this combination.
- To determine the overall survival of patients with AML and high-risk MDS treated with this combination.

2.1 BACKGROUND AND RATIONALE

2.2 AML and High-risk MDS in Older Patients:

AML is primarily a disease of older people with a median age of diagnosis of 68 years. There are approximately 13,000 new cases of AML per year in the United States and 55% of these occur in individuals who are age 65 years and older]. AMLin older patients is phenotypically different from AML in younger patients. As compared to their younger counterparts, older patients with AML more frequently have an antecedent hematological disorder or unfavorable cytogenetics, and respond less well to chemotherapy

Elderly patients with AML or high-risk MDS have a poor prognosis, which is attributed to having disease that is inherently more resistant to current standard cytotoxic agents and/or relatively poor tolerance of these agents because of comorbidity and reduced tolerance of adverse effects. As a result, despite steady progress in the therapy of AML in younger patients, treatment for elderly patients with AML has not improved for decades. Among patients 70 years or older and those with adverse karyotypes the 4-8 week mortality with intensive chemotherapy is 30%-50%, and the median survival is 4-7 months. Therefore such patients derive little benefit from intensive chemotherapy, and some may in fact be hanned with intensive chemotherapy. Such high induction mortality rates and poor tolerance to chemotherapy have resulted in a reluctance to treat AML in older patients. A Surveillance Epidemiology and End Results database analysis has indicated that 64% of AML patients over age 65 receive no therapy for AML, other than supportive care. This untreated group has a dismal median survival of 1.7 months.

These results emphasize the need to explore alternate strategies to intensive chemotherapy for AML and high-risk MDS in older patients and/or those unable to tolerate intensive chemotherapy (based on predicted high eight-week mortality rates of 30% or more). The development of novel and effective anti-AML agents and/or combinations is crucial to improving the outcome of older patients (age >/= 60) with AML. Therefore, we would like to evaluate the efficacy and tolerability of a novel combination ofvosaroxin in combination with decitabine in older patients with AML and high-risk MOS.

2.3 Vosaroxin (formerly voreloxin)

2.3.1 Rationale and Mechanism of Action:

Vosaroxin (formerly voreloxin) is a first-in-class anticancer quinolone derivative with a unique mechanism of action that appears to parallel the activity of the quinolone antibiotics in prokaryotes. Vosaroxin intercalates DNA and inhibits topoisomerase II activity through both enzymatic inhibition and direct poisoning [8, 9]. Vosaroxin preferentially targets actively replicating cells, and the extent of DNA damage is cell-cycle dependent with maximum activity in the G2/M phase. The DNA damage results in arrest at G2/M phase and cell death by apoptosis.

Vosaroxin is mechanistically similar to the anthracyclines such as idarubicin and daunorubicin, and the anthracenedione, mitoxantrone. However, in contrast to idarubicin and daunorubicin which are rapidly metabolized to the less active idarubicinol and daunorubicinol[10, 11], respectively; vosaroxin is minimally metabolized and does not require metabolism for cytotoxic activity. When administered on days 1 and 4 at 90 mg/m^2, concentrations ofvosaroxin are sustained above IC_5o for more than 7 days, with IC_{90} concentrations achieved for approximately 5 days.

Vosaroxin demonstrated potent anti-proliferative effects on human leukemic cell lines in vitro. Vosaroxin also demonstrated anti-proliferative activity in a phase I study in advanced hematologic malignancies (SP0-0004, completed in 2008)[12]. Two studies in AML have been completed, including a phase II study evaluating vosaroxin as a single agent in patients at least 60 years of age with previously untreated AML (SP0-0014)[13] and a phase Ib/II study evaluating the combination of vosaroxin with cytarabine in patients with relapsed or refractory AML (SP0-0012)[14]. The current Phase III, Randomized, Conh·olled, Double-Blind , Multinational Clinical Study of the Efficacy and Safety ofVosaroxin and Cytarabine Versus Placebo and Cytarabine in Patients With First Relapsed or Refractory Acute Myeloid Leukemia (VALOR) is ongoing. In this study vosaroxin is administered at a dose of90 mg/m^2 on days 1 and 4 for a total dose of 180 mg/m^2/cycle in combination with cytarabine 2-hour IV infusion of 1 g/m^2/day for 5 days. Vosaroxin was well tolerated at this dose. This dosing schema forms the basis for the vosaroxin dosing schedule we plan to use in our current protocol.

2.3.2 Pharmacodynamics, Pharmacokinetics and Preclinical Experience:

Vosaroxin demonstrated potent activity as a single agent on human leukemic cell lines in vitro, in AML patient bone marrow biopsies ex vivo, in hematologic xenograft models[8], and in a mouse model of marrow ablation[15].

The cytotoxic activity ofvosaroxin was evaluated in the human acute leukemia cell lines MV4-11, HL-60, and CCRF-CEM. The average half-maximal inhibitory concentration (IC_5o) values for vosaroxin in the myeloid leukemia cell lines, MV4-11 and HL-60, were 95±8 nM and 884± 114 nM, respectively. The acute lymphoblastic leukemia (ALL) cell line, CCRF-CEM, was also sensitive to vosaroxin, with an average IC_{50} of 166±0.4 nM.

Vosaroxin was highly active in two hematologic xenograft models, with 98% tumor growth inhibition of established tumors (Table 3). At maximum-tolerated dose (MTD), vosaroxin as a single agent ablated normal mouse bone marrow by 80% relative to vehicle control. This effect was reversible, with recovery of both marrow and peripheral blood counts.

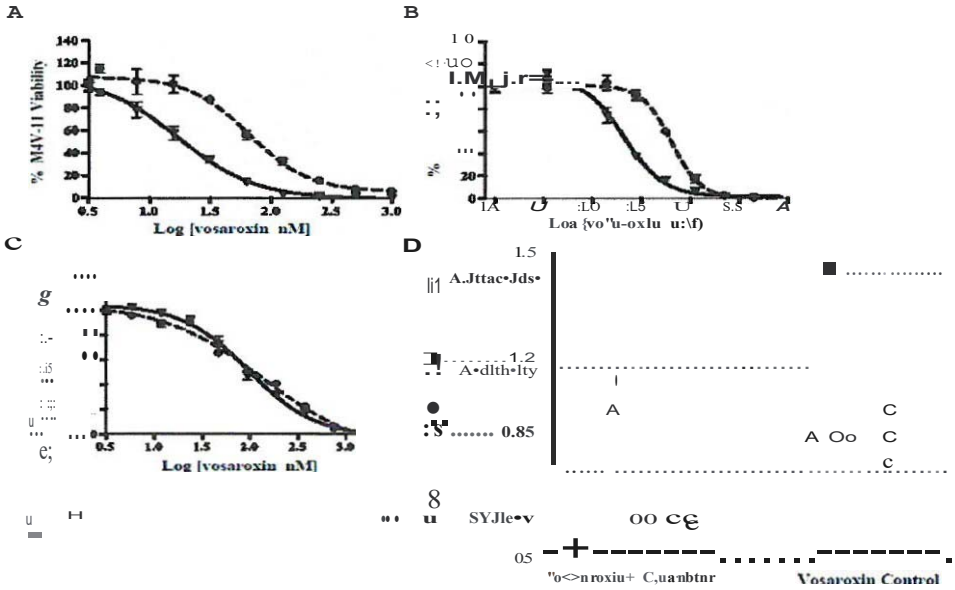
Tablel: Vosaroxin Tumor Growth Inhibition in Human Xenograft Cancer Models

Human Tumor	Vosaroxin Dose	Vosaroxin Schedule	CeU Line	Percent Inhib (1]	Survival [2]	Complete Response (3]
ALL	25 mglkg (75 mg/m^2)	IV. q7d>c:3	CCRF-CEM	98.1	6/6	0/6
Acute Lymphoma		IV.q 7d x 5	LM-3 Jck	99	6/6	4/6

Source: Hoell 2009.
Abbreviations: Inhib. inhibition:ALL. acme lymphoblastic leukemia:IV. imravenous: q7d, every 7 day.
[1] Values represem (1-average mmor weight treated /average rumor weight comrol) x 100%.
[2] (number surviving animal at end of study /number animals at beginning of study).
[3] (number of CR at end of smdy / mllllber animals at beginning of smdy).

The combination of an anthracycline with cytarabine is a standard of care treatment for AML. Therefore, studies were also undertaken to evaluate the effects of vosaroxin in combination with cytarabine in vitro and in vivo. The combination index method was used to assess the activity ofvosaroxin combined with cytarabine in acute leukemia cell lines in vitro (Figure 1). The combination resulted in synergistic activity in the myeloid leukemia cell lines, MV4-11 and HL-60, and additive activity in the ALL cell line, CCRF-CEM[15].

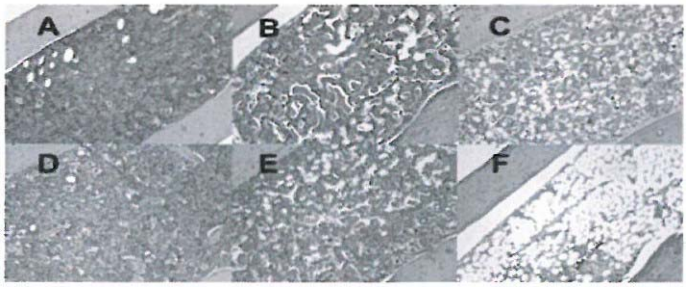
Figure 1. Vosaaoxin Combined \\'ith Cytarabine Has Additive or Synergistic Activity in Acute Leukemia Cell Lines



Sonrce: Scatenn 2010....
Assnys were perfonued with lnunan Acute leukemia cell lines reated with vo!.llroxin alone (•). or vosaroxin combined with cytnrabine ('"). Cells were exposed for 72 botus to senally diluted vosaroxin or vosaroxin and cytarabine. Viability is displayed as percent of vehicle control. A. MV4-11 :B. HL-60: and C. CCRF-CEM. D. The combin:nion mdex (CI) calculnted from the cwves inA-Cis displnyed CI < 0.85 indicates synergy. Cl 0.85-I .2 indicates ndclitivity. and Cl > 1.2 indicates antagonism. Each datn point represents an independent experiment. O. I\1V4-11: D. HL-60: .t;;..CCRF-CEJ\-1. Vosaroxin comrol is vosnroxin alone.

Vosaroxin and cytarabine were active as single agents and had supra-additive activity in combination in a normal mouse bone marrow ablation and recovery model that mimics the AML treatment paradigm[IS]. Animals received vosaroxin IV once daily or cytarabine IV 3 times daily, or both, on days 0 and 4. Bone marrow cellularity was reduced 80% in animals receiving vosaroxin at MTD and 26% in animals receiving cytarabine at MTD (Figure 2). The MTD of vosaroxin and cytarabine combined was 10 mg/kg vosaroxin (50% single-agent MTD) coadministered with 20 mg/kg cytarabine (33% single-agent MTD). At those doses, bone marrow cellularity was reduced 89% for the agents combined. Peripheral neutrophils and lymphocytes decreased following vosaroxin or cytarabine treatment alone or in combination; the effect on platelets was less profound. Both bone marrow cellularity and peripheral blood cell counts recovered to normal levels within 1 week, reflecting the recovery of hematopoiesis.

Figure 2. Vosaroxin and Cytarabine, Alone or in Combination, Ablate Norm 11 Bone farr·ow



Sotuce: Scatena 2010.[44]
CD-1 mice (n = 2-3) received vehicle.vosaroxin.cytarabine.or vosaroxin and cytarabine in combination on days 0 and 4. On day 6. femw-s were isolated and cellularity was assessed in H&E-stained bone man-ow sections (shown at 01iginal magnification x100). Ablation for vehicle-treated animals was subtracted from ablation of drug-treated animal!.. A. vehicle. 5% ablation: B. cytarabine at maximum-tolerated dose (MTD). 26'l-o ablation: C. vosaroxin at MTD. 80% ablation: D. cytarabine at 33% MTD.0% ablation: E. vosaroxin at 50% MTD.36% ablation: F. combination ofcytarabine at 33% MTD and vosaroxin at 50% MTD.89°'0 ablation.

The ex vivo evaluation of patient resistance to cytarabine and vosaroxin suggests a key role for vosaroxin in clinical activity and supports combination therapy. Patient bone marrow aspirates from both the single-agent study in newly diagnosed AML (SP0-0014) and the study of vosaroxin in combination with cytarabine in relapsed or refractory AML (SP0-0012) were evaluated for extreme drug resistance (EDR) ex vivo to vosaroxin and doxorubicin. Patient samples from SP0-0012 were also tested for EDR to cytarabine. Resistance to vosaroxin was profiled to evaluate whether clinical outcome correlated with ex vivo response. Doxorubicin was included as a comparator for both studies, as anthracyclines are commonly used to treat patients with AML. However, P-glycoprotein (P-gp) expression may affect response to anthracyclines as they are substrates for this efflux transporter. Vosaroxin is not a P-gp substrate[16], yet it acts through a similar but differentiable mechanism of action as anthracycline drugs.

Concentrations of 1 M and 3 M were used to characterize EDR for both vosaroxin and cytarabine, as these concentrations are observed in human plasma at the doses tested in SP0-0012. The concentrations tested for the anthracyclines were 0.1 f.!M doxorubicin and 0.05 M daunorubicin, levels that were sustained for 24 hours at clinically relevant doses[17, 18]. Daunomycin was also incorporated into the analysis, and 1 of 4 available samples from SP0-0012 had EDR to daunomycin.

Bone marrow aspirates were collected and assayed from 86 patients at baseline prior to dosing. Vosaroxin antiproliferative activity compared favorably with both cytarabine and doxorubicin, as shown in Table 2.

Table 2: Percentage of Bone Marrow Aspirate Samples With Extreme Drug Resistance to Vosaroxin and Other Common Chemotherapeutic Agents

			Extreme Drug Resistance	
Drug	Cone. (1)	OwraiJ ::'\=86	SP0-0014 Pre\iously rntrtated =37	SP0-0012 Rtlapstd or Rtfractoi' =49
Vosaroxin		27%	35%	20%
	3	2%	0%	4%
Cytarabine		ne	ne	73%
	:3	ne	ne	40% [I]
Doxorubicin	0.1	55% [2]	57%	53% [1]

TI1e Exiqon extreme dmg resistance (EDR®) assay was adapted to analyze proliferation ill hematologic samples using the luminescem Cell Titer Glo® proliferation assay (Promega Corporation). Assays were petfmmed at Exiqon Diagnostic:. (Tustin. CA). Exiqon defines EDR as < 50% inhibition of proliferation based on validation smdies in solid mmors.

Abbreviations: Cone., concentration: ne.not evaluated.

[1] For SP0-00 12.40 of 49 samples were analy7ed for EDR to 3 lM cytarabine.and 45 of 49 samples were evaluated for EDR to doxombici.J1.

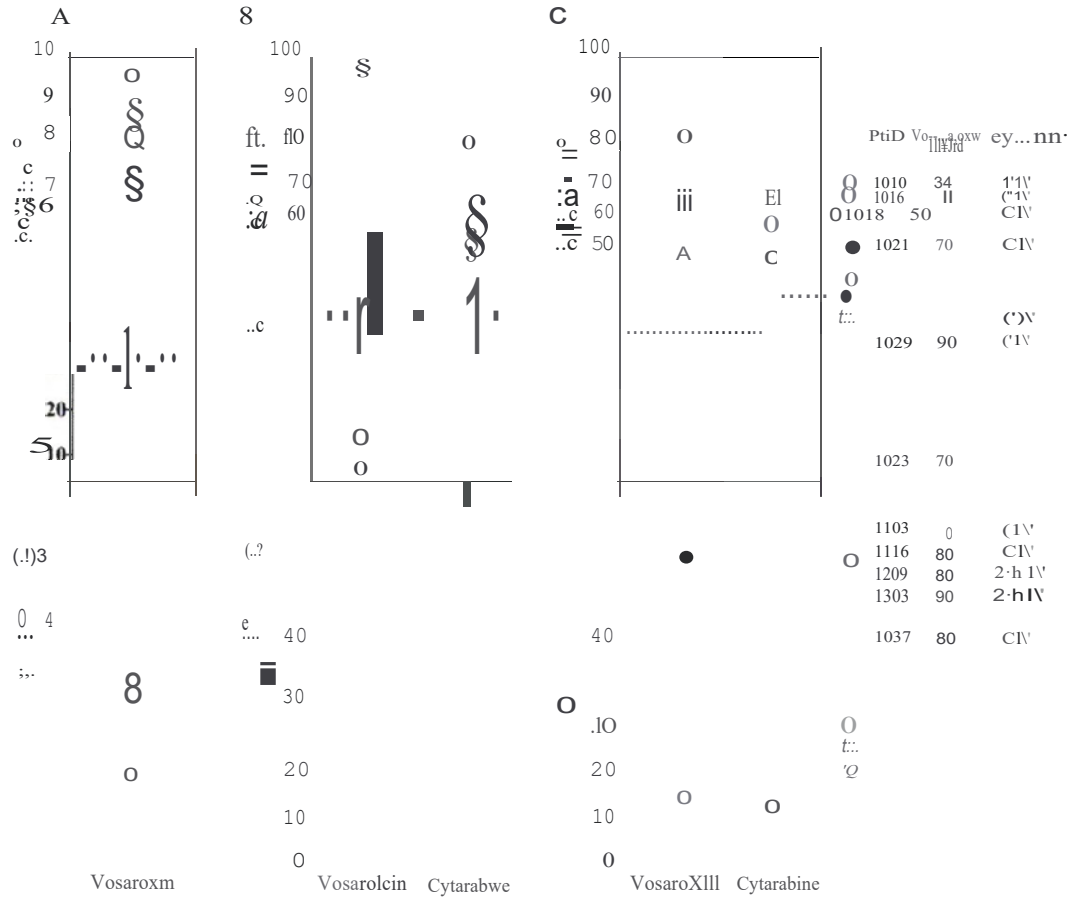
[2] Overall. 82 of 86 samples were evaluated for EDR ro doxombicin.

The assay is not validated to predict resistance for hematologic malignancies, but it does provide evidence that vosaroxin is a key contributor to response, and that the combination ofvosaroxin with cytarabine can potentiate the activity of each drug as a single agent. Patients from the single-agent study (SP0-0014) whose bone marrow aspirates were inhibited less than 46% by 1 j.tM vosaroxin had a greater chance of treatment failure ($p = 0.036$) than those whose aspirates were inhibited at least 46% (Figure 3A). The threshold value of 46% identified a significant difference in chance of treatment failure; 50% inhibition did not meet this criterion. Of the 8 patients with inhibition less than 46%, 7 (88%) experienced treatment failure. In contrast, of the 29 patients whose aspirates were inhibited at least 46%, 14 (48%) experienced treatment failure.

A similar analysis for the combination treatment study (SP0-0012) showed that most patients who responded met or exceeded the 46% threshold for vosaroxin, in contrast to cytarabine (Figure 3B). Eleven patients who had post-treatment CRs had bone marrow aspirates at baseline (predose) for evaluation ofEDR, defined here as less than 46% inhibition of proliferation. As shown in Figure 3C, 2 of the 11 patient samples had EDR to 1 j.tM vosaroxin, 6 had EDR to I j.tM cytarabine, and 1 was resistant to both. Taken together, these data suggest that vosaroxin is a major contributor to the observed clinical CRs, given the limited ex vivo resistance to vosaroxin in the presence of ex vivo resistance to cytarabine in patients subsequently treated with the combination. Furthermore, these data suggest enhanced activity of the combination treatment, as 7 of 11 patients in remission had EDR ex vivo to cytarabine, vosaroxin, or both. In agreement

with these data, vosaroxin combined with cytarabine had synergistic activity in 22 of25 samples from patients with primary AML treated ex vivo with the drugs[19].

Figure 3. Patients in Complete Remission May Have Extreme Drug Resistance to Cytarabine, Vosaroxin, or Both, Suggesting Enhanced Activity in Combination



Bone manow aspirates were collected at baseline and analyzed at Exiqon Diagnostics in the luminescent Cell Titer-Glo® proliferation assay (Promega Co1poration). Hatched line indicates 46% inhibition of proliferation. The threshold value of 46% identified a significant difference in chance of treatment failure: 50% inhibition did not meet this c1iterion.

A. Assay of a<>pirates fi:om SP0-0014 patients (single-agent vosaroxin) showing percent growth inhibition by 1 t•M vosaroxin. O Treatment faihu:e: + complere remission (C'R).

B. Assay of aspirares from SP0-0012 patiems (vosaroxin in combination wirb cytarabine) showing: percent growth inhibition by 1 vosaroxin and 1 11M cytarabine. O Treatment faihue: + C'R

C'. Assay of aspirates from SP0-0012 patienrs in C'R showing percent growth inhibition by 1 tM vosaroxin and 1 pM cytarabine using the same symbol for each individual patient. Cytarabine C'IV is a continuous intravenous (IV) infi.lsion for 24 homs ar 400 mg/m^2/day for 5 days: 2-h IV is a 2-hour IV infusion at 1 g/m^2/day for 5 days.

Details of additional nonclinical studies of vosaroxin are presented in the vosaroxin investigator brochure (IB).

2.2.3 Clinical Experience:

No clinical studies combining vosaroxin with decitabine have been conducted as of yet. Ours will be the first clinical trial to evaluate the efficacy and tolerability of this novel combination. However, clinical data and toxicity profiles from the SP0-0012; a phase lblll dose-escalation study of two dose regimens (schedules) ofvosaroxin in combination with cytarabine in patients

with relapsed or refractory AML are available and will be briefly discussed. These may serve as a possible guide to efficacy and toxicity profiles we may anticipate in our study.

The enrollment for study SP0-0012; a phase Ib/ll dose-escalation study of two dose regimens (schedules) ofvosaroxin in combination with cytarabine in patients with relapsed or refractory AML is complete (110 patients) and patients are in follow-up[20]. Data from this study provide the preliminary safety and clinical activity information for combination treatment, and formed the basis for the pivotal phase III VALOR study of vosaroxin in combination with cytarabine. SP0-0012 had two phases: dose escalation (phase Ib) and dose expansion at the MTD (phase II). In phase II, patients either had first relapsed AML (relapse following an initial CR 3 months and S 24 months) or primary refractory AML (failed to achieve a CR or CRp [CR with incomplete platelet recovery] following 1 or more cycles of induction, or an initial CR < 3 months). Treatment was with 80 or 90 mg/m^2 vosaroxin on days 1 and 4 in combination with cytarabine either as a continuous intravenous (CIV) infusion (400 mg/m^2/day) on days 1-5 or a 2-hour intravenous (IV) infusion (1 g/m^2/day) on days 1-5. Characteristics ofthe 69 patients treated in phase 2 are shown in Table 3. Clinical activity endpoints are shown in Table 4. A summary of grade 3 or greater treatment-emergent adverse events (TEAEs) with more than 10% incidence by regimen is shown in Table 5.

Table 3: Study Population Characteristics in Phase 2 of SP0-0012 (N = 69)

	First Relapse (I\= 36)	Primary Refractory (I\ = 33)
0\'eraU Population = 69 (1])	52%	48%
Initial C'R < 12 months (N = 23)	33%	na
Initial C'R 12-24 months (N = 13)	I9%	na
Median duration of initial CR months (range)	7.3 (3.3-23.7)	na
Median prior induction cycles (range)	na	2 (1-6)
Median age. years (range)	61 (35-73)	57.5 (18.5-71)
z 60 years	64%	34%
ECOG 0-1	89%	85%
Cytogenetics per NCCN Practice Guidelines 2010		
Favorable	3%	3%
Intermediate	64%	58%
Unfavorable	28%	21%

Data source: ASCO/EHA 2010 poster presentations.[49,S6]
Abbreviations: CR.complete remission:na, not applicable: ECOG. Eastem Cooperative Oncology Group: NCCN. National Comprehensive Cancer Network.
[I] Patients;vere treated \vith vosaroxin at 80 or 90 mg/m^2 on days I, 4 and cyrarabine 400 mg/m^2 CIV or 1 glm- IV on days 1-5.

Table 4: Clinical Activity ofVosaroxin (80 to 90 mg/m2} and Cytarabine Combination Treatment in Phase 2 of SP0-0012

Endpoint	Outrome
CR rate	17 of69 (25%)
Combined CR rare (CR+CRp+CRi)	20 of69 (29%)
Primaty refractoty	6 CR. 1 CRp
First relapse	
Initial CR < 12 months	4CR
Initial CR 12-24 months	7 CR. 1 CRp. 1 CRi
Leukemia-free mvival. days (95% CI) [I]	
Overall	329 (222. nr)
Primaty refi:act01y	nr (260. nr)
First relapse	329 (175. m)
Median overall s\uvival. days (95% CI)	
•\11	2 16 (140.307)
First relapse	2 18 (131. 377)
Ptimaty refractory	209 (124.307)

Data source: ASCO/EHA 2010 poster presentations_4Y.SU At the time of data cutoff (May 20 10). 20 patients were in follow-up.
Abbreviations: CR. complete remission: CRp.CR with incomplete platelet recovety:CRi.CR with incomplete recovery of platelets or neutrophils: CI. confidence intetval:nr. not reached.
[1] Time from complete remission (CR. CRp. CRi) to relapse or death.
Patients were treated with vosaroxin at 80 or 90 mg/m^2 on days 1.4 and cytarabine 400 mg/m^2 CIV or 1 m^2 IV on days 1-5.

Table 5: All Treatment-Emergent Adverse Events Grade 3 by Regimen for Patients Treated With Vosaroxin at 80 to 90 mg/m2 in Combination With Cytarabine in Phase 2 of SP0-_0012 (N=69)

	Cytarabine Regimen		
Advtrst Evtnt	CIV (:\" = 30)	2-Hour IV (N = 38)	OvtraU (N=68)
Upper GI mucositis [I]	20%	11%	15%
Febrile neutropenia	53%	34%	43%
Sepsis/Bacteremia [1]	30%	24%	27%
Infections [1]	10%	13%	12%
Pneumonia [1]	17%	8%	12%
Hypoka lemia	27%	13%	19%
Hypophosphatemia	13%	0%	6%

Data source: ASCO/EHA 2010 poster presentations.[4,6]
Abbreviation : CIV.continuous intravenous: IV, inn-aveuous: GI. gastrointestinal.
[1] Aggregates of multiple prefelTed tenus.
Patients were treated with vosaroxin at 80 or 90 mg/m^2 on days 1.4 and cytarabine 400 mg/m^2 CIV or 1 g/m^2 IV on days 1-5.

2.2.4 Dosing and Schedule:

How supplied:
Vosaroxin is a clear, colorless to pale-yellow liquid formulated for IV administration manufactured in accordance with current Good Manufacturing Practices (GMP). Vosaroxin vials may contain either 100 mg or 230 mg vosaroxin at a concentration of 10 mg/mL. Each milliliter also contains 45 mg ofD-sorbitol to maintain isotonicity. Methanesulfonic acid is added to assist in the solubilization ofvosaroxin. The sterile nonpyrogenic solution is formulated without preservatives.

Packaging and Labeling:
Vosaroxin injection is supplied in single use vials, either 10 mL or 25 mL Type 1 glass vials labeled as vosaroxin. The product is packaged in boxes (kits) that contain vosaroxin and appropriate number of sterile 0.22 11m filters.

At minimum, the label of each vial and other packaging will include the following information, consistent with country-specific regulations as appropriate:

Vosaroxin Protocol number Product code and lot number Content: 1vial of either 10 mL or25 mL s lution ofVosaroxin (10 mg/mL) for intravenous administration only Sterile single use vial only Administer as directed in the protocol Protect from light Store in an upright position Do not store above 25°C Manufacture date, expiration date, or use-by date (as applicable) Caution statement Sunesis Pharmaceuticals, Inc., 395 Oyster Point Blvd., Suite 400 South San Francisco, CA 94080 USA Tel: (650) 266-3500

Disposal of unused/ expired drug:
Unused/ expired vosaroxin will be disposed per MD Anderson policy.

Storage:
Vosaroxin vials must be stored as packaged in an upright position at room temperature. Thermostatically controlled storage conditions consistent with United States Pharmacopeia (USP)-defined "Controlled Room Temperature" are recommended.

Vosaroxin must not be frozen or stored in a refrigerator. When vosaroxin is drawn

into a syringe, stability data support a maximum of 2 hours exposure to continuous ambient light. If the syringe containing the product is completely wrapped in foil or other protective covering from ultraviolet and visible light (eg, amber bag, brown paper bag), this 2-hour stability maximum can be extended up to 24 hours. The pharmacy manual has more information on storage conditions.

Preparation and Administration of Vosaroxin

Undiluted vosaroxin should be administered before the infusion of decitabine according to these general guidelines:

- Wear gloves and adhere to strict aseptic technique.
- Inspect the vial and confirm it is not cracked or damaged in any way.
- Inspect the solution and confirm it is not discolored and contains no visible particulates.
- Do not infuse vosaroxin in the same IV line (tubing) with sodium chloride solutions or other medications. The product may precipitate in sodium chloride solutions. If no alternative line is available, flush the line thoroughly with 5% dextrose in water (D5W) before and after administration.

Suggested Procedure for Preparation:

1. Calculate the dose according to protocol or pharmacy manual instructions.

2. Attach the provided 0.22 fliD sterile filter unit to the tip of the sterile plastic syringe that will be used to administer vosaroxin.

3. Attach an appropriate gauge needle to the filter unit.

4. Withdraw the proper dose from the vosaroxin vial into the syringe.

5. Discard the used filter unit and needle and cap the syringe.

6. Protect the filled, capped syringe from light until ready to administer .

Suggested Procedure for Administration :

1. A bilurnenal or trilurnenal catheter is recommended. Start an IV infusion through one of the lumens using D5W or analogous solution available locally such as Glucose Intravenous Infusion BP 5% at a slow rate sufficient to keep the vein open ("keep

vein open"rate).

2. Before administering vosaroxin, increase the D5W infusion rate to approximately 100 mL/hour, and continue this rate during the vosaroxin infusion.

3. Administer vosaroxin via syringe by accessing an available hub or stopcock.

4. Administer vosaroxin as a short infusion over **approximately** 8 to 10 minutes, either manually or using a syringe pump **with a + 20-25 minute window to allow for flushing time as reflected in documentation.**
5. At the end of the infusion, flush the IV line with D5W per institutional standard.

6. If a central catheter or heparin Jock is in place, it may be capped according to the study site's usual procedures.

Vosaroxin is not known to be a vesicant or irritant. If extravasation is observed or suspected, treat according to standard institutional procedures

2.3 Decitabine (DAC)

2.3.1 Rationale and Mechanism of Action:

Decitabine (Dacogen®, 5-aza-2'-deoxycytidine) is an analogue of the natural nucleoside 2'-deoxycytidine. It exerts its antineoplastic effects after phosphorylation and direct incorporation into DNA and inhibition of DNA methyltransferase, causing hypomethylation of DNA and cellular differentiation or apoptosis. Decitabine inhibits DNA methylation *in vitro,* which is achieved at concentrations that do not cause major suppression of DNA synthesis. In rapidly dividing cells, the cytotoxicity of decitabine may also be attributed to the formation of covalent adducts between DNA methyltransferase and decitabine incorporated into DNA. Non-proliferating cells are relatively insensitive to decitabine[21-23].

2.3.2 Pharmacodynamics, Pharmacokinetics and Preclinical Experience:

Decitabine has been extensively studied in humans. After IV injection pharmacokinetics of decitabine, using bioassay to measure drug concentration, has been characterized by a two compartmental body model , with a $t^{1/2}$ of the distribution phase of 7 minutes[24, 25]. The terminal phase $t^{1/2}$ was between 10 and 35 minutes and a mean volume of distribution of 4.6 L/kg. Decitabine is rapidly metabolized by deamination by liver cytidine deaminase. Mean total plasma clearance was 126 mL/minlkg. Renal excretion ofunmetabolized decitabine was quite low, less than 1% of the total dose.

Decitabine does not block the progression of G1-phase cells into S-phase or the progression of S-phase cells to mitosis, as measured by the incorporation of radioactive thymidine into DNA and by autoradiography, which suggests that the cytotoxic action of decitabine is not self-limiting[24]. Exposure time appears to be an important factor relative to the cytotoxicity produced by decitabine. Greater cytotoxicity was produced at longer rather than shorter exposure times for both experimental leukemic cell lines and tumor cells[26, 27]. Exposure of cells to decitabine during the first cell cycle produced minimal growth inhibition, whereas increasing the exposure time to two or more cell cycles resulted in an increased inhibition of cell growth[27, 28]. Further, there is an optimal concentration at which analogs of 5-azacytosine induce cellular differentiation; higher concentrations produce less differentiation and more cytotoxicity.

Decitabine's mechanism of action, hypomethylation of DNA followed by stimulation of gene expression and cell differentiation, is a relatively new approach to cancer treatment. Decitabine has shown considerable activity against various types of experimental leukemias[29-31]. In in vivo comparative studies, decitabine showed greater activity than cytarabine. In addition, decitabine has considerable antitumor activity in vitro and in in vivo animal tumor systems, exceeding that of structurally analogous compounds, such as cytarabine. Clinical experience with decitabine confinned that it produces an antineoplastic effect in acute leukemia, chronic leukemia, and myelodysplastic syndrome and its differentiation-inducing properties have been confirmed in vivo in humans.

2.3.3 Clinical Experience:

Multiple phase I and II studies using decitabine as a therapy for leukemia have been reported. The first studies were in acute myeloid leukemia (AML) and acute lymphocytic leukemia (ALL). Rivard et al.[32] conducted the first study with decitabine as a single agent for remission induction in pediatric patients with refractory or relapsed leukemia. Dose-dependent activity was noted in this first small study, which was followed by another small study[33]. A response rate of 37%, based on 22% complete response (CR) and 15% partial response (PR) was noted in this second study, along with 48% hematological improvement (HI). Several subsequent studies of decitabine as a single agent have also demonstrated efficacy in the treatment of AML and ALL[34]. Combination studies included decitabine with amsacrine[35], idarubicin[35], and daunorubicin[36]. Response rates were generally higher in relapsed than in refractory disease[34] and lower in heavily pretreated patients[37].

Decitabine has been approved by the Food and Drug Administration (FDA) in the United States for treatment of patients with MDS including previously treated and untreated, *de novo* and secondary MDS[38]. Decitabine has been reported to have anti-leukemic activity in AML. In a phase II study in elderly patients (2: 60 years) with previously untreated AML, decitabine resulted in a complete remission rate of24% with a median overall survival of7.7 months, and a 30-day mortality rate of 7%[39]. In this study decitabine was administered at a dose of20 mg/m^2 intravenously for 5 consecutive days of a 4-week cycle. The most common toxicities were myelosuppression, febrile neutropenia, and fatigue.

2.3.4 Dosing and Schedule:

How Supplied:
Decitabine is supplied as a lyophilized white to almost white, finely crystalline, odorless powder for injection in 20mL vial glass vials, containing 50 mg of decitabine, monobasic potassium phosphate, and sodium hydroxide.

Storage:
The intact vials should be stored at room temperature (15-30 oc; 59-86°F)

Stability: Shelf life surveillance of the intact vials is on-going. The intact vials are stable for at least 1 year at room temperature (22- 25°C), 2 years at 2-8°C or 6 months at 40° C.

Reconstitution and dilution of the powder for injection (with 1OmL of sterile water for injection) results in a rapidly decomposing solution. The concentration of decitabine in the reconstituted and diluted solution decreases about 10% after 4 hours at 25°C or about 10% after 24 hours at 4°C. Since 10% is the maximum allowable decomposition, and the solution will also decompose during administration (infusion), the solution should be prepared just prior to administration. Unless used within 15 minutes of reconstitution, the diluted solution must be prepared using cold (2-8°C) infusion fluids and stored at 2-8°C for a maximum of up to 7 hours until administration. This solution can be infused over a maximum period of 3 hours.

Preparation and administration:
When reconstituted with 10 mL of sterile water for injection each mL will contain 5 mg of decitabine, 6.8 mg ofKH2P04, and approximately 1.1 mg NaOH. The pH of the resulting solution is 6.5- 7.5. The reconstituted solution can be further diluted to a concentration of 1 mglmL or 0.1 mglmL in cold infusion fluids (0.9% Sodium Chloride Injection USP, 5% Dextrose in Water Injection, USP, or Lactated Ringer's Injection USP).

Decitabine is to be administered as a continuous intravenous infusion over approximately one hour.

Drug handling precautions will be strictly followed. Skin contact with the solution should be avoided and protective gloves should be worn. Drug spilling can be inactivated by 2 M sodium hydroxide solution. The skin should be treated with a borax buffer solution pH 10 and after that thoroughly washed with water and soap.

Drug supply and distribution:
Decitabine is commercially available from EISAI, Inc and will be obtained commercially and charged to patient's account. Detailed instructions for its use may be found in the pharmacy manual.

Reported Adverse Events and Potential Risks:
Autoimmune reaction (antiplatelet antibodies, erythema nodosum), decreased hemoglobin, decreased leukocytes (total WBC), decreased neutrophils/granulocytes (ANC/AGC), decreased platelets, fatigue (lethargy, malaise, asthenia), alopecia, diarrhea, peritonitis, nausea, vomiting, anorexia, stomatitis/pharyngitis (oral/pharyngeal, mucositis), increase bilirubin, increased SGOT (AST) (serum glutamic oxaloacetic transaminase), increased SGPT (ALT) (serum glutamic pyruvic transaminase), liver damage, depressed level of consciousness, abdominal pain or cramping.
The following adverse events have been reported in decitabine trials:: allergic reaction; allergic rhinitis ;GVHD; bone marrow cellularity; atrial fibrillation; cardiac ischemia/infarction; cardiopulmonary arrest; hypotension; left ventricular systolic dysfunction; right ventricular dysfunction; fever; insomnia; rigors/chills; weight loss; pruritus; rash; anal ulcer; ascites; constipation; distension; esophagitis; GI obstruction; ileus; taste alteration; CNS hemorrhage; GI hemorrhage; lung hemorrhage; nose hemorrhage; petechiae; urinary hemorrhage; cholecystitis; liver dysfunction/failure; infection without neutropenia; opportunistic infection; perianal abscess; head/neck edema; alkaline phosphatase; creatinine; hypercalcemia; hyponatremia; fracture; agitation; CNS ischemia; confusion; depression; dizziness; extrapyramidaVinvoluntary movement; motor neuropathy; psychosis; seizure; sensory neuropathy; bone pain; headache; muscle pain; urinary pain; ARDS; bronchospasm; cough; dyspnea; hiccoughs; pneumonitis/pulmonary infiltrates; cystitis; renal failure; urinary frequency; phlebitis; thrombosis/thrombus/embolism; veno-occlusive disease.

2.4 Rationale for Combined Treatment with Vosaroxin and Decitabine:

Standard treatment for patients diagnosed with acute myeloid leukemia (AML) comprises of two chemotherapy phases, induction and consolidation[40]. Such an approach is curative for younger patients or those with favourable cytogenetics but is rarely curative for older patients (65 years) or those with unfavourable cytogenetics. Older patients have dismal CR rates (24% to 33%), increased risk of induction mortality (29%) and high rate ofleukemia relapse[41, 42]. Thus, new safe and effective therapies are urgently needed for older patients and/or patients unable to tolerate standard therapy.

Vosaroxin and decitabine have non-overlapping primary molecular mechanisms of action. Vosaroxin targets the topoisomerase II and results in G2/M phase arrest and apoptosis. In contrast to vosaroxin, decitabine inhibits the DNA-methyltransferase activity resulting in hypomethylation and cell cell cycle arrest at the G1 phase via p21(WAF1) and the G2/M phase via the p38 MAP kinase pathway[43]. The non-confluent safety profile ofvosaroxin and decitabine (refer to respective toxicity profiles under section 2.2.3 and 2.3.4) and their unique and non-overlapping anti-leukemic activities make them well suited for frontline combination therapy in elderly patients and/or patients unable to tolerate standard therapy for AML or high-risk MDS.

3.1 STUDY DESIGN AND ELIGIBILTIY:

3.2 Study Design:

This will be a single ann, single center, open label study of the combination of vosaroxin with decitabine in previously untreated patients with acute myeloid leukemia or high-risk myelodysplastic syndrome who are elderly (age 2 60) and/or unable to tolerate standard therapy. The study will consist of a lead-in phase Ib01tion to determine the safe dose of vosaroxin in combination with decitabine to move into the phase IIportion of the study. A total of up to 84 evaluable patients (including up to 24 patients in the run-in phase I and up to 60 patients in the phase II) will be treated on this protocol.

In the initial portion (Phase I) we will treat 6 patients with vosaroxin administered intravenously on days 1 and 4 at a dose of 90 mg/m^2 in the first cycle (induction 1) for a total dose of 180 mg/m^2/cycle in combination with decitabine at a dose of20 mg/m^2 intravenously for 5 consecutive day (Days 1 to 5). These doses have been given safely in previous studies as follows. A vosaroxin dose of 90mg/m2 was identified as the MTD in the dose-escalation (phase Ib) of the SP0-0012 study. In the phase II of this study 69 patients who had either first relapsed AML (relapse following an initial CR 3 months and :s; 24 months) or primary refractory AML (failed to achieve a CR or CRp [CR with incomplete platelet recovery] following 1or more cycles of induction, or an initial CR < 3 months) were treated with 80 or 90 mg/m2 vosaroxin on days 1and 4 in combination with cytarabine either as a continuous intravenous (CIV) infusion (400 mg/m2/day) on days 1-5 or a 2-hour intravenous (IV) infusion (1 g/m2/day) on days 1-5. The combination of vosaroxin at a dose of 90mg/m2 and IV cytarabine was well tolerated. Data from the SP0-0012 study provide the preliminary safety and clinical activity information for combination treatment, and formed the basis for the pivotal phase Ill VALOR study of vosaroxin in combination with cytarabine which is currently ongoing. Decitabine has been approved for treatment of MDS and AML at a dose of 20 mg/m2/day for days 1-5. Decitabine is less cytotoxic, less myelosuppressive and has lower incidence of mucositis than IV cytarabine which has safely been administaered in combination with vosaroxin in the SP0-0012 and VALOR studies. Therefore, we anticipate that a starting dose of vosarxoin administered intravenously on days 1and 4 at a dose of 90 mg/m2 in the first cycle (induction 1) for a total dose of 180mg/m2/cycle in combination with decitabine at a dose of 20 mg/m2 intravenously for 5 consecutive day (Days 1to 5) would be a reasonable optionThese doses have been given safely in previous studies. The purpose of the lead-in phase Ib portion is to ensure safety. If clinically significant, study drug related grade 3-4 toxicity is observed during the first cycle in 1 or less of 6 evaluable patients treated, the study will transit to the Phase II portion. If clinically significant, study drug related grade 3-4 toxicity is observed during the first cycle in 2 or more of 6 evaluable patients treated, six additional patients will be treated on the Phase Ib portion at a lower dose level (see section 4.4 and section 10.2) until we define a Phase II safe dose schedule at which 1 or less out of 6 evaluable patients on the Phase I experience clinically significant, study drug related grade 3-4 toxicity during the first cycle. After the Phase I portion ensures safety thereby defining the Phase IIdose schedule, all subsequent patients will receive the same dose schedule in the Phase IIportion. This Phase IIportion will include up to a total of 60 evaluable patients.

The primary endpoint of the Phase II portion is overall response rate. Overall response rate = CR + CRp + CRi. Early stopping rules will be implemented for low ORR rates (see section 10.2).

3.3 **Patient Eligibility:**

3.3.1 Inclusion Criteria:

1) Previously untreated AML (>/= 20% blasts). Patients with high-risk MDS (defined as having >/= 10% blasts in the bone marrow) or patients with Chronic Myelomonocytic Leukemia (having >/= 10% blasts in the bone marrow) may also be eligible after discussion with Principal Investigator (PI). Prior therapy with hydroxyurea, biological or targeted therapy (e.g. FLT3 inhibitors, other kinase inhibitors), or hematopoietic growth factors is allowed, however prior therapy with chemotherapy agents for the disease under study is not allowed. Patients may have received one dose of cytarabine (up to 2 g/m^2) administered at presentation for control ofhyperleucocytosis.
   For patients with prior MDS or Chronic Myelomonocytic Leukemia who transformed to AML, therapy received for MDS is not considered as prior therapy for AML.

2) Age >/= 60 years and not candidates for conventional cytotoxic chemotherapy or refuse it; OR patients below the age of 60 years who are considered unfit and/or unable to tolerate standard chemotherapy at the discretion of the treating physician or the principal investigator.

3) Eastern Cooperative Oncology Group perfonn ance status </= 2. {Appendix D)

4) Adequate hepatic (serum total bilirubin </= 1.5 x upper limit normal (ULN), alanine aminotransferase and/or aspartate transaminase </= 2.5 x ULN) and renal function (creatinine </= 2.0 mg/dL).

5) Left ventricular ejection fraction (LVEF) at least 40% by multiple gated acquisition (MUGA) scan or echocardiogram (ECHO)

6) Patients must be willing and able to review, understand, and provide written consent before starting therapy.

7) Females must be surgically or biologically sterile or postmenopausal (amenon·heic for at least 12 months) or if of childbearing potential, must have a negative serum pregnancy test within 14 days before the start of the treatment. Women of childbearing potential may have a urine pregnancy test, instead of a serum pregnancy test. If either the serum or urine pregnancy test is equivocally negative the patient will be eligible for the protocol.

Women of childbearing potential must agree to use an adequate method of contraception during the study until 30 days after the last treatment. Males must be surgically or biologically sterile or agree to use an adequate method of contraception during the study until 30 days after the last treatment.

3.2.2 Exclusion Criteria:

I) New York Heart Association class III or IV heart disease, active ischemia or any other uncontrolled
cardiac condition such as active angina pectoris, clinically significant cardiac arrhythmia that requires therapy in the opinion of the treating physician or PI, uncontrolled hypertension (blood pressure > 160 systolic and > 110 diastolic not responsive to antihypertensive medication), uncontrolled diabetes mellitus in the opinion of the treating physician or PI, or uncontrolled congestive heart failure in the opinion of the treating physician or PI.

2) Myocardial infarction in the previous 12 weeks (from the start of treatment).

3) Active and uncontrolled disease/infection as judged by the treating physician.

4) Pregnant or breastfeeding

5) Known Human Immunodeficiency Virus seropositivity

6) Any other medical, psychological, or social condition that may interfere with study participation or compliance, or compromise patient safety in the opinion of the investigator or medical monitor

7) Acute promyelocytic leukemia (APL).

4.1 TREATMENT PLAN:

4.2 Treatment Plan in Phase I and II:

In Phase I six patients will be treated with vosaroxin administered intravenously on days 1 and 4 at a dose of 90 mg/m^2 for a total dose of 180 mg/m^2/cycle in combination with decitabine at a dose of20 mg/m^2 intravenously on days 1 through 5. Patients will be assessed for non-hematological toxicities during the first 28 days on therapy and for hematological toxicities for the first 42 days on therapy. The purpose of the lead-in Phase I portion is to ensure safety. If first cycle DLT is observed in 1 or less of 6 patients treated this dose level will be the MTD and the study will transit to the Phase II portion. A summary and rationale for continuation of treatment

will be submitted to investigational new drug (IND) office for review. Cohort summaries will also be submitted when going to a lower dose cohort in phase I. Once approved, the Phase II portion of the study will be opened. Up to 60 patients will be treated on the Phase II portion. The primary endpoint of the Phase II study will be efficacy as measured by ORR rate. Early stopping rules will be implemented for excessive toxicity or lack of efficacy. Please refer to statistical section 10.2 for details.

4.2 General Study Treatment Plan:

All chemotherapy infusions will be done at MDACC only. The intent of the study design is for all patients to receive up to 7 courses, including up to two courses of induction therapy and up to five courses of consolidation therapy. Treatment will be continued during the duration of the study unless patients exhibit evidence of treatment failure, disease progression, experience an unacceptable toxicity, or the investigator determines that discontinuation of treatment is in the best interest of the patient. Patients will be treated with study drugs based on a calculation determined from the patient's body surface area (BSA). BSA will be calculated before each cycle and will be based on the patient's height (measured at baseline) and weight (measured each cycle). Dosing of both drugs will be based on actual body weight with no capping of dose based on BSA.

4.3 Induction Therapy in Phase 1:

The first 6 patients on study (first cohort) will receive 1 or 2 induction cycles of therapy according to the following starting schedule: vosaroxin will be administered intravenously as a short infusion over 8 to 10 minutes on days 1 and 4 at a dose of 90 mg/m^2 in the first cycle (induction 1) for a total dose of 180 mg/m^2/cycle in combination with decitabine at a dose of20 mg/m^2 administered as a continuous intravenous infusion over approximately 1 hour given daily for 5 consecutive days (Days 1 to 5). These doses have been given safely in previous studies. If a dose is missed, the patient may take the missed dose if it has been less than 48 hours.

Patients, who have not achieved remission (CR, CRp, Cri) following the initial induction (induction I) course, can receive one additional induction course (induction 2) at the same dose as induction 1 to optimize response if indicated. The re-induction must be given within 4-8 weeks of documented refractory leukemia. Re-induction (Induction 2) may be given beyond the stipulated 8 weeks if approved by the study PI.

If the bone marrow aspirate and/or biopsy(s) perfonned after the induction courses reveal a remission marrow (CR/CRp/CRi), then the patient may proceed to consolidation therapy at the discretion of the treating investigator. In addition, any clinically significant drug-related, nonhematologic toxicity experienced by a patient should return to < grade 2 or the baseline grade before the patient continues treatment.

Should the patient not achieve CR/CRp/CRi after the second induction course, they will be taken off study unless clinical benefit is observed and the PI approves continuation of therapy on the protocol.

Hydroxyurea 1.5 g orally daily for up to 10 days is allowed in the first induction course for white blood count >30.0 x 10^9/L.

4.4 Defmition of Dose Limiting Toxicities and Criteria in Phase 1:

Dose limiting toxicities will be according to the NCI CTEP criteria Common Terminology Criteria for Adverse Events version 4.0[44]. A non-hematologic dose-limiting toxicity (DLT) is defined as a clinically significant (as assessed by treating physician) grade 3 or 4 adverse event or abnormal laboratory value (according to CTCAE criteria) assessed by treating physician as related to study drug (and unrelated to disease progression, intercurrent illness, or concomitant medications) occurring during the first 28 days on study. A hematologic DLT is defined as severe myelosuppression with a hypoplastic marrow with less than 5% cellularity and no evidence ofleukemia 42 days from start of therapy. This will define severe and delayed myelosuppression not related to persistent leukemia and likely related to treatment.

The purpose of the lead-in Phase I portion is to ensure safety. If first cycle DLT is observed in 1 or less of 6 evaluable patients treated, this dose level will be considered the MTD and the study will transit to the Phase II portion. If first cycle DLT is observed in 2 or more of 6 evaluable patients treated, 6 additional patients will be treated on the Phase I portion at a lower dose level as detailed below until we define a Phase II dose schedule (MTD) at which 1 or less out of 6 patients on the Phase I experience first cycle DLT. After the Phase I portion ensures safety thereby defining the Phase II dose schedule, all subsequent patients will receive the same dose schedule in the Phase II portion.

a. The first 6 patients on study (Phase I portion of study) will receive vosaroxin IV on days 1 and 4 at a dose of90 mg/m^2 in the first cycle (induction 1) for a total dose of 180 mg/m^2/cycle in combination with decitabine at a dose of 20 mg/m^2 intravenously for 5 consecutive days (Days 1 to 5). IfDLT's are observed in 0-1/6 in phase I, this dose level will be considered to be the MTD for this study and the study will open broadly for the Phase II at this dose schedule.

b. IfDLT's are observed in 2/6 or more patients, this dose level would exceed the MTD, and the induction chemotherapy dose will be reduced to vosaroxin at a dose of 70 mg/m^2 IV on days 1 and 4 in the first cycle (induction I) for a total dose of 140 mg/m^2/cycle in combination with decitabine at a dose of 20 mg/m^2 intravenously for 5 consecutive days (Days 1 to 5). Six patients will be treated to evaluate the safety ofthis schedule, and after consultation with and approval of the Pl. IfDLTs are observed in 0-116 in phase I, the study will open broadly for the phase II at this schedule at this dose schedule.

c. IfDLT's are observed in 2/6 or more patients, this dose level would exceed the MTD, and the induction chemotherapy dose will be reduced to vosaroxin at a dose of 50 mg/m^2 IV on days 1 and 4 in the first cycle (induction 1) for a total dose of 100 mg/m^2/cycle in combination with

decitabine at a dose of 20 mg/m^2 intravenously for 5 consecutive days (Days 1 to 5). Six patients will treated to evaluate the safety of this schedule, and after consultation with and approval of the Pl. If DLTs are observed in 0-1/6 in phase I, the study will open broadly for the phase II at this schedule at this dose schedule.

d. If DLT's are observed in 2/6 or more patients, this dose level would exceed the MTD, and the induction chemotherapy dose will be reduced to vosaroxin at a dose of 50 mg/m^2 IV on days 1 and 4 in the first cycle (induction 1) for a total dose of 100 mg/m^2/cycle and the decitabine will be reduced to 20 mg/m^2 IV for only 4 consecutive days (Days 1 to 4). Six patients will be treated to evaluate the safety of this schedule, and after consultation with and approval of the PI. If DLTs are observed in 0-1/6 in phase I, the study will open broadly for the phase II at this schedule at this dose schedule.

After the first 6 subjects have been treated with vosaroxin and decitabine at the selected MTD (either dose-level a, b, cor d), and assessed for toxicity, a summary and rationale to continue enrollment will be provided by the study team to the IND Office including a separate cohort summary for each dose level tested. These will be reviewed by the IND Office Medical Monitor. The IND Office Medical Monitor will indicate whether the study may continue enrollment.

4.5 Induction Therapy in Phase II:

Following the phase I portion to ensure safety, all subsequent patients will receive the following induction regimen (induction 1):

a. Vosaroxin intravenously on days 1 and 4 at a dose of70 mg/m^2 for a total dose of 140 mg/m^2/cycle (days 1 and 4), or the final induction dose (MTD) determined in phase I.

b. Decitabine IV at a dose of20 mg/m^2 for 5 consecutive days (days 1 to 5), or the final induction dose (MTD) determined in phase I.

The 70mg/m2 day 1 and 4 dosage ofvosaroxin has been implemented in the REVEAL-I study (single agent vosaroxin in elderly AML) and was felt to be as efficacious as the 90 mg/m2 dose with a lower incidence of mucositis. Based on our current experience and the data from REVEAL 1 we would like to request IND approval to reduce the vosaroxin induction dose from 90 mg/m2 days 1 and 4 to 70 mg/m2 days 1 and 4 with the intention of decreasing toxicity while maintaining equivalent efficacy.

Treatment may be repeated every 4-7 weeks. If a dose is missed, the patient may take dose the missed dose if it has been less than 48 hours.

Patients, who have not achieved any response (CR, CRp, Cri) following the initial induction (induction 1) course, can receive one additional induction course (induction 2) at the same dose as induction 1 or other dose modifications for re-induction may be made in the best interest

of patient after discussion with the PI to optimize response if indicated. The re-induction must be given within 4-8 weeks of documented refractory leukemia. Re-induction (Induction 2) may be given beyond the stipulated 8 weeks if approved by the study Pl.

If the bone marrow aspirate and/or biopsy(s) performed after the induction courses reveal a remission marrow (CR/CRp/CRi), then the patient may proceed to consolidation therapy at the discretion of the treating investigator. In addition, any clinically significant drug-related, nonhematologic toxicity experienced by a patient should return to < grade 2 or the baseline grade before the patient continues treatment.

Should the patient not achieve CR/CRp/CRi after the second induction course, they will be taken off study unless clinical benefit is observed and the PI approves continuation of therapy on the protocol.

Hydroxyurea 1.5 g orally dail for up to 10 days is allowed in the first induction course for white blood count >30.0 x 10 /L.

4.6 Post-remission Therapy in Phaseland Phase II:

Patients achieving a CR/CRp/CRi may receive consolidation/ maintenance therapy as follows:

Consolidation - Up to 5 additional cycles as follows:

a. Vosaroxin intravenously on days 1 and 4 at a dose of70 mg/m^2 for a total dose of 140 mg/m^2/cycle (days 1 and 4). Decitabine at a dose of20 mg/m^2 intravenously for 5 consecutive days (days 1-5), or the final induction dose determined in phase I.

Patients who achieve a CR/CRp/CRi should receive the consolidation cycle no sooner than 28 days from Day 1 of the previous induction or re-induction cycle provided their peripheral blood counts have recovered (ANC >/= 1.0 x 10^9/L and platelet count >/= 50 x 10^9/L). If patient has documented CRp they may proceed with consolidation cycles even if the platelet count remains </= 50 x 10^9/L if approved by the PI. If patient has documented CRi they may proceed with consolidation cycles even if the platelet count remains </= 50 x 10^9/L and/or ANC </= 1.0 x 10^9/L if approved by the Pl.

If the peripheral count recovery is delayed beyond 42 days from Day 1 of the prior induction or re-induction cycle and the delay is presumed to be secondary to the induction therapy, the study drug doses for the consolidation must be reduced as follows: reduce the dose of vosaroxin to 50mg/m^2 IV on days 1 and 4 for a total dose of 100 mg/m^2/cycle in combination with decitabine at a dose of 20 mg/m^2 intravenously for 5 consecutive days (Days 1 to 5).

Consolidation cycles to be given every 4-8 weeks upon recovery of counts and toxicities. Consolidation cycles may be given beyond the stipulated 8 weeks if approved by the study Pl.

If the patient experienced a dose modification during induction, the patient may remain at the modified dose level or return to the original dosing schedule during consolidation as determined to be in the patient's best interest by the treating physician and Pl. Dose adjustments to the subsequent cycles of the consolidation schedule will depend on toxicity with previous courses. Dose adjustments felt to be in the best interest of the patient are allowed but must be discussed with PI and the discussion documented in the patient's medical record. For clinically significant, study regimen related grade 3-4 toxicities, reduce the dose ofvosaroxin to 50 mg/m^2 *Non* days 1 and 4 for a total dose of 100 mg/m^2/cycle in combination with decitabine at a dose of20 mg/m^2 intravenously for 5 consecutive days (Days 1 to 5). If Grade 3 or 4 toxicities recur or persist at this lower dose, reduce the dose of vosaroxin to 50 mg/m^2 IV on days 1 and 4 for a total dose of 100 mg/m^2/cycle in combination with decitabine at a dose of 20 mg/m^2 intravenously for 4 consecutive days (Days 1 to 4). If Grade 3 or 4 toxicities recur or persist at this lower dose, reduce the dose of vosaroxin to 50 mg/m^2 IV on days 1 and 4 for a total dose of 100 mg/m^2/cycle and reduce the decitabine to 20 mg/m^2 *N* for only 3 consecutive days (Days 1 to 3)

Other dose modifications may be petmitted if in the patient's best interest after discussion with the Principal Investigator and the discussion documented in the patient's medical record. Vosaroxin may be omitted in consolidation cycles for patients in CR/Cri/CRp based on their toxicity in the first cycle, asjudged by the treating physician, and only after discussion with the Pl. Up to a total of 7 cycles of induction-consolidation will be given (up to 2 induction cycles and up to 5 consolidation cycles).

4.7 Management of Toxicities and Dose Modifications:

4.7.1 Induction, Re-Induction, and Consolidation Cycles:

All dose delays, reductions, and modifications for hematologic and non-hematologic toxicities will be assessed according to sections 4.7.2 and 4.7.3.

4.7.2 Hematologic (Blood/Bone marrow) Toxicity:

No dose reductions, delays, or modifications are required for hematologic toxicities during the induction or re-induction cycles. It is assumed that low counts at diagnosis are due to involvement by the disease process and require therapy for improvement. Likewise, patients who are considered for re-induction have persistent disease and thus no recovery of hematologic parameters can be expected. Patients who achieve a CRJCRp/CRi should receive the consolidation cycle no sooner than 28 days from Day 1 of the previous induction or re-induction cycle, provided their peripheral blood counts have recovered (ANC >/= 1.0 x 10^9/L and platelet count >/= 50 x 10^9/L). If patient has documented CR they may proceed with consolidation cycles even if the platelet count remains </= 50 x 10 /L if approved by the Pl. If patient has documented CRi they may proceed with consolidation cycles even if the platelet count remains </= 50 x 10^9/L and/or ANC </= 1.0 x 10^9/L if approved by the Pl. If the peripheral count recovery is delayed beyond 42 days from Day 1 of the prior induction or re-induction cycle and

the delay is presumed to be secondary to the induction therapy, the study drug doses for the consolidation must be reduced as follows: reduce the dose of vosaroxin by one dose level as described in section 4.7.4in combination with decitabine at a dose of20 mg/m^2 intravenously for 5 consecutive days (Days 1 to 5).

4.7.3 Non-hematologic Toxicity:

If clinically significant grade 2 toxicity occurs during a course of induction or consolidation therapy, and it is unresponsive to optimal treatment and is thought to be possibly related to vosaroxin treahnent, vosaroxin treatment may be withheld after the onset of an event until the adverse event (AE) has returned to baseline or </= grade 1. If the AE has returned to baseline or </= grade 1 within the 5-day induction or 5-day consolidation treatment interval from the start of therapy, treahnent may resume at the same dose, but missed doses will not be made up. If the AE has returned to </= grade 1 before administration of the next cycle, no dose reductions will be made with subsequent cycles.

If grade 3 or greater toxicity occurs during a course of induction or consolidation therapy, and it is unresponsive to optimal treatment and is thought to be possibly related to vosaroxin treatment, vosaroxin treatment may be withheld after the onset of an event until the AE has returned to baseline or </= grade 1. If the AE has returned to baseline or </= grade 1 within the 5-day induction or 5-day consolidation treatment interval from the start of therapy, treatment may resume but at a reduced dose.. Reduce the dose ofvosaroxin by one dose level as described in section 4.7.4 for the day 4 dosage of that cycle only. Missed doses will not be made up. In subsequent cycles of therapy, the dose ofvosaroxin will remain at the reduced dose level for each subsequent cycle in combination with decitabine at a dose of 20 mg/m^2 intravenously for 5 consecutive days (Days 1 to 5). If the toxicity recurs or persists in spite of reducing the vosaroxin dose to, further dose reductions as outlined in section 4.7.4 will be allowed. If the toxicity recurs or persists after reducing to the lowest dose level, as described in section 4.7.4, then no further dose reductions will be pennitted and the patient will be taken off study unless otherwise discussed with the Pl.

If persistent grade 2 toxicity occurs after completion of a cycle of therapy (i.e., after day 5 of an induction treatment cycle or day 5 of a consolidation treatment cycle), and it is unresponsive to optimal treatment and is thought to be possibly related to vosaroxin treatment, vosaroxin treahnent may be delayed up to 21 days after the onset of an event or until the AE has returned to baseline or S grade 1. Then administer 100% of the planned dose. If toxicity persists longer than 21 days or recurs, the vosaroxin dose may be delayed and the dose of vosaroxin will be reduced as specified in section 4.7.4. Additional dose reductions can be performed, as specified in section4.7.4, if toxicity recurs or persists during induction or consolidation treatment cycles respectively.. If the toxicity recurs or persists after reducing to the lowest level as outlined in section 4.7.4, then further dose reductions will not be permitted and the patient will be taken off study unless otherwise discussed with the PI. .

If grade 2:3 toxicity occurs after completion of the vosaroxin treatment (i.e., after day 5 of an induction treatment cycle or day 5 of a maintenance treatment cycle), and it is suspected that vosaroxin played a role in toxicity, the next scheduled cycle of vosaroxin therapy should be withheld until toxicity returns to grade 0 or 1 or to baseline. The dose of vosaroxin for each subsequent cycle will be reduced as specified in section 4.7.4. Additional dose reductions can be performed, as specified in section 4.7.4, if the toxicity recurs or persists.. If the toxicity recurs or persists after reducing to the lowest dose level, then further dose reductions will not be permitted and the patient will be taken off study unless otherwise discussed with the Pl.

For those patients who are receiving consolidation cycles of Decitabine with no Vosaroxin, as discussed in section 4.6, dose adjustments will be allowed based on the discretion of the treating physician. The Dose adjustments for the Decitabine will follow the same dose adjustments listed in section 4.7.4.

Dose modifications different from those stated in the protocol will be evaluated by the principal investigator and the sponsor -MDACC IND office and may only be allowed after approval by Pl.

Dose modifications for the patients in CR who are deemed eligible to continue on decitabine only after the first induction cycle will be done at the discretion of the treating physician but only after discussion with the PI.

Adverse events which are moderate to severe in intensity and which are assessed as possibly or probably related to study drug, may result in the termination of study treatment in the affected study patient. Such termination should be reviewed with the PI at the earliest possible time. Following review with the PI, the study patient may be permanentl y withdrawn from the study depending upon the nature and severity of the event.

4.7.4 Dose Modifications

Dose Modifications

Dose Level	Vosaroxin	Decitabine
	Dl &D4	
-3	50 mg/m2	20 mg/m2 (Days 1 - 3)
-2	50 mg/m2	20 mg/m2 (Days 1 -4)

-1	50 mg/m2	20 mg/m2 (Days 1-5)
0	70mg/m2	20 mg/m2 (Days 1-5)

4.7.5 Supportive Care:

Supportive care measures including blood products, infection prophylaxis and growth factors will be administered according to institutional and Leukemia Department guidelines.

4.7.6 Concomitant Medications:

Concomitant medications are recommended as prophylaxis for nausea, vomiting, and infections, and are allowed for managing myelosuppression as shown in Table 6. Myelosuppression is expected in patients with AML due to underlying disease, as well as due to chemotherapy (such as vosaroxin and decitabine), or both. Most patients have neutropenia, thrombocytopenia, or both at study entry. Myelosuppression may be managed with growth factor support and blood transfusion according to institutional standard of care, American Society of Clinical Oncology (ASCO) Practice Guidelines, and NCCN Practice Guidelines.

Infections secondary to myelosuppression are common in patients with AML, and may be related to underlying disease, chemotherapy, or both. Therefore, the use of prophylactic antibiotics, antifungal agents, and antiviral agents is recommended. A suggested regimen is ciprofloxacin (500 mg po q 12h), fluconazole (200 mg po qd), and acyclovir (800 mg po q 12h). One dose of prophylactic intrathecal chemotherapy will be allowed with diagnostic lumbar puncture.

All ongoing medications and therapies (including herbal products, nutritional supplements, and nontraditional medications) at screening will be considered prior medications. Concomitant medication data will not be collected or entered into the case report form; however, the subject's medication record will contain a list of concomitant medications. Patients will discontinue study treatment if they intentionally receive or require treatment with a medication prohibited by the protocol. If however prohibited medication is inadvertently administered/ taken by the patient, the patient may remain on study as long as the prohibited medication is discontinued as soon as feasible. End-of-treatment procedures will be performed, and follow-up will commence. Prohibited medications are shown in Table 6.

Table 6: Instructions for the use of concomitant medications and therapies

Category of Use	Medication	Comment on Use	Restriction on Use
Recommended	Prophylactic antibiotics, antifungal agents, and antiviral agents	Strongly encouraged	None
	Antiemetic agents	According to standard of care at MDACC	None
Allowed	Oral allopurinol or rasburicase	At investigators discretion	None
	Intrathecal chemotherapy	At investigators discretion	One dose of low-dose cytarabine or methotrexate with diagnostic LP
	Leukapheresis	According to standard of care at MDACC	Before induction 1 day 1 only
	Red blood cell transfusion	None	None
	Platelet transfusion	None	None
	White blood cell transfusion	At investigators discretion according to standard of care at MDACC	None
	Myeloid growth factors	At investigators discretion according to standard of care at MDACC	None
	Erythropoetin or darbepoetin	At investigators discretion	None
	Any other medication for supportive care	At investigators discretion according to standard of care at MDACC	None
Prohibited	Hydroxyurea	Hydroxyurea at a dose </= 1.5 g orally daily for up to 10 days is allowed in the first induction course for WBC >30.0 x 10^9/L.	Hydroxyurea cannot be used beyond day 10 of induction 1

MDACC = MD Anderson Cancer Center

5.0 PRETREATMENT EVALUATION:

History and physical exam including measurement of height, weight, and vital signs (blood pressure, heart rate, temperature, and breathing rate) and performance status, CBC with differential and platelets, chemistry profile (total bilirubin, serum creatinine, SGPT or SOOT, uric acid, LDH, potassium, magnesium, glucose), and ECG within 14 days oftherapy initiation.

ECHO or MUGA within 28 days prior to treatment start.

Women of childbearing potential must have a negative serum or urine pregnancy test within 3 days before receiving the first dose of study drug.

Bone marrow aspirate and/or biopsy within 28 days of therapy start The bone marrow evaluation will include immunophenotyping by flow cytometry and cytogenetic studies.

6.1 EVALUATIONS:

6.2 Evaluations During Study:

Patient will have physical examination prior to each course. CBC with differential and platelet counts at least once a week until remission (CR/CRp/CRi), then every 1 to 2 weeks during active treatment, and every 4 to 8 weeks thereafter as long as on study. No differential is needed if the WBC is $< 1.0 \times 10^9$/L. The patients in CR who are deemed eligible to continue on decitabine only will need to have physical examination after every 2-3 courses of decitabine.

Chemistry profile at least weekly until remission, then every 2 to 4 weeks during active treatment.

For those patients who are receiving Decitabine alone without Vosaroxin, as outlined in section 4.6, these patients may receive Decitabine with a local physician but will be required to return to MDACC every two to three cycles for a physical exam.

The patient may have the laboratory work done at a local clinic and the results reported to the research nurse for the study. The laboratory work done at the local clinic will be forwarded to the patient's attending physician at MDACC or PI of the study, who will sign off on the labs to verify that the results have been reviewed.

Outside Physician Participation During Treatment

1. MDACC Physician communication with the outside physician is required prior to the patient returning to the local physician.

This will be documented in the patient record

2. A letter to the local physician outlining the patient's participation in a clinical trial will request local physician agreement to supervise the patient's care (Appendix H)
3. Protocol required evaluations outside MDACC will be documented by telephone, fax ore-mail. Fax and/or e-mail will be dated and signed by the MDACC physician, indicating that they have reviewed it.
4. Changes in drug dose and/or schedule must be discussed with and approved by the MDACC physician investigator, or their representative prior to initiation, and will be documented in the patient record.
5. A copy of the informed consent, protocol abstract, treatment schema and evaluation during treatment will be provided to the local physician.
6. Documentation to be provided by the local physician will include drug administration records, progress notes, reports of protocol required laboratory and diagnostic studies and documentation of any hospitalizations.
7. The home physician will be requested to report to the MDACC physician investigator all life threatening events within 24 hours of documented occurrence.

Bone marrow aspirate and/or biopsy starting on day 21 (+/- 7 days) of therapy and then every 4 weeks(+/- 7 days) as required by leukemia evolution until confirmation of remission (CR/CRp/CRi) or nonresponse. Bone marrow evaluations to include immunophenotyping by flow cytometry and cytogenetics at the discretion of the treating physician.

Bone marrow tests can be ordered more frequently if mandated by development of peripheral blood counts. No repeat bone marrow is necessary if nonresponse or progressive disease can be unequivocally diagnosed from peripheral blood tests or, in patients with a WBC < 0.3 if the bone marrow test is considered noncontributory by the investigator at any time point. Patient will be followed for survival at MD Anderson Cancer Center (MDACC) every 3 to 6 months for up to 5 years after completion of active treatment and while still on study. If the patient is unable to return to MDACC the follow-up visits may be conducted via telephone.

Concomitant medication data will not be collected or entered into the case report form; however, the subject's medication record will contain a list of concomitant medications.

Data regarding adverse events will be collected during the study. Please see **Appendix E** regarding data capturing of adverse events and adverse events source documentation. Protocol specific data will be entered into PDMS/CORe. PDMS/CORe will be used as the electronic case report form for this protocol. Only unexpected AEs will be recorded in the Case Report Form (CRF). The Principal Investigator will sign and date the AE log per each patient at the completion of each course. Following signature, the AE log will be used as source documentation for the adverse events for attribution.

Treatment may be discontinued for a variety of reasons, including patient withdrawal, investigator decision, and reasons specified by the protocol. Reasons for discontinuation of treatments are described below.

6.2 **Follow-up Evaluations:**

After completion of induction and consolidation treatment patients will continue to be followed at MDACC for 5 years.

Every 4-8 weeks, blood will be drawn for routine standard of care tests. If the patient cannot return to the MDACC clinic for blood draws, the blood draws can be set up at a local clinic closer to the patient's residence and the results reported to the research nurse for the study. The laboratory work done at the local clinic will be forwarded to the patient's attending physician at MDACC or PI of the study, who will sign off on the labs to verify that the results have been reviewed

Every 3-6 months, patients will be scheduled for clinic visits for clinical evaluation and physical examinations. If the patient cannot make it to the MDACC clinic for these visits, the patient can be followed by a local physician. The local physician will perfonn the physical examination and the records will be forwarded to MDACC.

7.1 DISCONTINUATION OF TREATMENT :

7.2 Discontinuation Criteria for Individual Patients

7.2.1 Patient Withdrawal

Patients may voluntarily withdraw consent to participate in the clinical study at any time and without giving any reason. Their withdrawal will not jeopardize their relationship with their healthcare providers or affect their future care. Patients may also choose to withdraw from study treatment, but agree to remain in the study for follow-up procedures.

7.2.2 Investigator Discontinuation of Patient

The investigator may exercise medical judgment to discontinue study treatment if clinically significant changes in clinical status or laboratory values are noted.

7.2.3 Criteria for Protocoi-Defmed Required Discontinuation of Treatment

The protocol requires discontinuation of study treatment for the following reasons:

1. Patient requests discontinuation.

2. There is unacceptable toxicity (i.e., NCI CTCAE version 4.0 clinically significant grade 4 drug-related non hematologic toxicity).

3. Patient experiences an NCI CTCAE version 4.0 >/= grade 3 drug-related non-hematologic toxicity or clinically significant infection of any grade that is not recovered by Day 75 from the onset of the toxicity.

4. Patient experiences a third occurrence of an NCI CTCAE version 4.0 clinically significant grade 3 drug related non-hematologic toxicity.

5. Patient experiences study drug related asymptomatic grade 2 total bilirubin or creatinine abnormality that is not recovered by Day 75 from the onset of the toxicity.

6. There is a need for any treatment not allowed by the protocol.

7. Treatment failure or disease relapses. Patients may continue if they are determined to have clinical benefit following discussion with the PI and the treating Physician. The discussion will be documented in the medical record.

8. Investigator discretion.

7.2.4 Follow-Up at Treatment Discontinuation or Early Withdrawal

Patients who discontinue treatment for any reason will complete end-of-treatment procedures. End of treatment procedures will include a CBC with differential and platelets and a limited chemistry profile (total bilirubin, serum creatinine, SGPT or SGOT, potassium, magnesium, glucose). A bone marrow aspiration may be recommended only if non-response or progressive disease cannot be unequivocally diagnosed from peripheral blood. Although treatment will be discontinued at that time, all patients who do not withdraw consent for follow-up, die, or become lost to follow-up, will remain on study for follow-up evaluations. Subject will be followed for toxicity for at least 30 days after the last protocol treatment. The 30 day follow-up visit will be scheduled as a clinic visits for clinical evaluation and physical examinations. If the patient cannot make it to the MDACC clinic for this visit,the required follow up treatment procedure s may be done with a local physician and the records forwarded to MDACC. The research nurse will contact the patient by telephone and get a verbal assessment of the patient' s condition. The phone conversation will then be documented in the patients charts.

7.2 **Study Stopping Rules**

The principal investigator and MDACC IND office have the right to tenninate this clinical study at any time. The principal investigator and MDACC IND office, as appropriate, will be involved in any decisions regarding tenninating the study, temporarily suspending enrollment, or stopping ongoing treatment with study treatment.

Reasons for te1minating the clinical study or a study site's participation include, but are not limited to, the following:

- The incidence or severity of an adverse reaction related to treatment in this study or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory
- Data recording is inaccurate or incomplete
- Study site personnel are noncompliant with study procedures

7.3 **Protocol Violations and Deviations**

Protocol violations are defined as significant departures from protocol-required processes or procedures that affect patient safety or benefit potential, or confound assessments of safety or clinical activity. A protocol deviation is a departure from the protocol that does not meet the above criteria. Protocol violations or deviations may be grouped into the following classes:

- Enrollment criteria
- Study activities (missed evaluations or visits)
- Noncompliance with dose or schedule, including dose calculation, administration, interruption, reduction, or delay; or discontinuation criteria
- Investigational product handling, including storage and accountability
- Informed consent and ethical issues

8.0 CRITERIA FOR RESPONSE

8.1 Complete response (CR)

- Peripheral blood counts:

  Neutrophil count 2: 1.0×10^9/L

  Platelet count 2: 100×10^9/L

- Bone marrow aspirate and biopsy

  :S5% blasts

- No extramedullary leukemia

8.2 Complete response without platelet recovery (CRp)

- Response as in CR but platelets $< 100 \times 10^9$/L

8.3 CR with insufficient hematological recovery (platelets or neutrophils) (CRi)

- Response as in CR but platelets $<100 \times 10^9$/L or neutrophils $< 1 \times 10^9$

8.4 Overall Response rate (ORR) = CR + CRp + CRi

8.5 Disease-free survival (DFS)

Time from CR, CRp or CRi until the date of first objective documentation of disease-relapse or death.

8.6 Overall survival (OS)

- Time from date of treatment start until date of death due to any cause

9.1 REGULATORY AND REPORTIN G REQUIREMENTS

Adverse event reporting will be as per the NCI criteria and the MDACC Leukemia Specific Adverse Event Recording and Reporting Guidelines.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) most current version will be utilized for adverse event reporting. (http://ctep.cancer.gov /reporting/ctc.html)[44). (Appendix F)

9.2 **Expedited Adverse Event Reporting:**

Refer to **Appendix E** for Leukemia-Specific Adverse Event Recording and Reporting Guidelines. Protocol specific data will be entered into PDMS/CORe. PDMS/CORe will be used as the electronic case report form for this protocol. Only unexpected AEs will be recorded in the Case Report Fonn (CRF). The Principal Investigator will sign and date the AE log per each patient at the completion of each course. Following signature, the AE log will be used as source documentation for the adverse events for attribution.

These guidelines serve to bring the Department of Leukemia in compliance with the institutional policy on Reporting of Serious Adverse Events-definition of expected AE- "All clinical protocols should include a list of the expected and anticipated events or hospitalizations relating to the study treatment"and Guideline for Good Clinical Practice 4.11.1 "All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting".

Adverse event is any untoward medical occurrence that may present during treatment with a phannaceutical product but which does not necessarily have a causal relationship with this treatment.

Adverse drug reaction is a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function.

Assessing causal connections between agents and disease is fundamental to the understanding of adverse drug reactions. In general, a drug may be considered a contributory cause of an adverse event if, had the drug not been administered, 1) the event would not have happened at all, 2) the event would have occurred later than it actually did, or 3) the event would have been less severe.

Adverse Events (AEs) will be evaluated according to current CTCAE version in each protocol. Only unexpected AEs will be recorded in the Case Report Form (CRF).

Adverse events which are moderate to severe in intensity and which are assessed as possibly or probably related to study drug, may result in the tennination of study treatment in the affected study patient. Such termination should be reviewed with the principal investigator at the earliest possible time. Following review with the principal investigator, the study patient may be permanently withdrawn from the study depending upon the nature and severity of the event.

Expected events during leukemia therapy are:

1. Myelosuppression related events (due to disease or leukemia therapy):

a. febrile or infection episodes not requiring management in the intensive care unit

b. epistaxis or bleeding except for catastrophic CNS or pulmonary hemorrhage

c. anemia, neutropenia, lymphopenia, thrombocytopenia, leukopenia, leukocytosis

2. Disease related events:

a. symptoms associated with anemia

i. fatigue

ii. weakness

iii. shortness of breath

b. electrolyte abnormalities (sodium, potassium, bicarbonate, C02, magnesium)

c. chemistry abnormalities (LDH, phosphorus, calcium, BUN, protein, albumin, uric acid, alkaline phosphatase, glucose)

d. coagulation abnormalities

e. disease specific therapy (induction, maintenance, salvage, or stem cell therapy)

f alopecia

g. bone, joint, or muscle pain

h. liver function test abnormalities associated with infection or disease progression

i. disease progr ession

3. General therapy related events:

a. catheter related events

b. renalfailure related to tumor lysis syndrome or antibiotic/antifungal

therapy

c. rash related to antibiotic use

4. Hospitalization for the management ofany of the above expected events

Abnonnal hematologic values will not be recorded on the CRF. For abnormal chemical values grade 3 or 4, the apogee will be reported per course in the CRF.

9.3 Serious Adverse Event Reporting:

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience- any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threat ening, or require hospitali zation may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsion s that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defmed above may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.

- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedure s outlined in "University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected , must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

- All life-threatening or fatal events, that are unexpected, and related to the study drug, must have a written report submitted within 24 hours (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.

  Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.

- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

(Please see Appendix E regarding data capturing of adverse events and adverse events source documentation.)

9.4 Serious Adverse Event Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices , the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

9.4 Serious Adverse event Reporting to Sunesis Inc.

The assigned research staff will send via fax a courtesy copy of the MD Anderson electronic SAE form within the timeframe specified in the protocol but will not answer sponsor queries associated with these SAEs.

10.1 STATISTICS

10.2 Sample size

This will be a single arm, single center, open label study of the combination ofvosaroxin with decitabine as an induction therapy in previously untreated patients with acute myeloid leukemia (AML) or high risk myelodysplastic syndrome (MDS) who are elderly (age 2: 60) and/or unable to tolerate standard therapy. A total of up to 84 patients will be enrolled in the study.

Phase I

A total of up to 24 patients will be accrued into the Phase I part.

Phase II

A total of up to 60 patients (including 6 patients treated at the MTD from the Phase I part) will be recruited for the Phase II part.

The primary efficacy endpoint is overall response rate (ORR). ORR = CR + CRp + CRi. Responses will be evaluated at the end of the first induction cycle and second induction cycle (if a second induction cycle is needed). With a null hypothesis of 40% historical response rate, a sample size of 60 patients would be required to demonstrate a response rate of 60% for the combination ofvosaroxin and decitabine using a one-sample exact binomial test and with a two-sided alpha of 0.05 and a power of 82%.

10.3 Statistical Design

Phase I

. In phase I portion of the study the MTD is defined as the highest daily oral dose evaluated at which <33% of patients experience a DLT. Six patients will be treated. If clinically significant drug related Grade 3-4 toxicity is observed during the first cycle in 0-1 patient out of 6 patients, this will define a safe schedule and the study will open broadly for the Phase II portion. If drug related Grade 3-4 toxicity is observed in 2 or more of 6 patients, this dose will exceed DLT, and a lower dose schedule will be investigated in an additional 6 patients. Please refer to Section 4.4. The dosing algorithm is presented in Table?.

Table7.Dosing algorithm

Dose Level	\ osaroxin D1&D4	Decitabine
-3	50mg/mL	20 mg/m2 (Days 1-4)
-2	50 mg/m^2	20 mg/m2 (Days 1 – 5)
-1	70 mg/m^2	20 mg/m^2 (Days I – 5)
0	90mg/m^2	20 mg/m^2 (Days 1 – 5)

Phase II

Efficacy

The historical data suggested an ORR of 40% and with the assumption that the improved ORR is 60% the study will be stopped early if the observed patients' data suggest that:

$$\Pr(n > 0.6 \text{ data}) < 0.025$$

Here n is the overall response rate (ORR). That is, if at any time during the study we determine that there is a less than 2.5% chance that the average ORR is greater than 60%, we will terminate the study. The ORR is assumed to follow a non-informative prior of Beta (1.2, 0.8). The stopping boundaries for ORR, based on these assumptions and monitoring conditions are found in table 8. We will apply these stopping boundaries starting from the fifth patient and in cohorts of 5. For example, accrual will cease if only 2 or less than 2 patients experience overall response among the first 10 patients treated. The operating characteristics are summarized in table8.

Table 8.Stopping boundaries for ORR

Number of patients evaluated	5	10	15	20	25	30	35	40	45	50	55	60

for response												
Number of patients with response (i.e., CR, CRp or CRi)	0	0-2	3-5	6-7	8-9	10-12	13-15	13-17	18-20	21-22	23-25	26-28

Table 9. Operating characteristics for monitoring of overall response rate

True overall Response Rate	Early Stopping Probability	Sample size 25%, 50%, 75%		
0.35	0.974	10	15	30
0.40	0.888	15	20	35
0.45	0.702	15	35	60
0.50	0.442	30	60	60
0.55	0.209	60	60	60
0.60	0.079	60	60	60
0.65	0.027	60	60	60

Toxicity Monitoring

Following are the rules for the monitoring of toxicities in the Phase II portion of the study. Toxicity will be defined as clinically significant non-hematologic drug related grade 3 or higher adverse events. The probability of toxicity is denoted by PE. We assume PE – beta (0.6, 1.4). Our stopping rule is given by the following probability statement: Probability (PE > 0.30 | data)>0.975. That is, we will stop the study if, at any time during the study, we determine that there is more than 97.5% chance that the toxicity is more than 30%. This stopping rule will be applied in each cohort. The stopping boundaries for clinically significant toxicities observed during the first cycle, based on these assumptions and monitoring conditions found in table 10. We will apply these stopping boundaries starting from the fifth patient and in cohorts of 5. For example, accrual will cease if 4 patients experience clinically significant toxicities during the first cycle among the first 5 patients treated. The operating characteristics are summarized in table 11.

Table 10. Stopping boundaries for Phase II toxicities

The number of patients evaluated fortoxicities	5	10	15	20	25	30	35	40	45	50	55	60
The number of patients with DLTs	4	5-6	7-8	9-10	11-12	13-14	15-16	17-18	19	20-21	22-23	24-25

Table 11. Operating characteristics

True Toxicity Rate	Early Stopping Probability	Sample Size		
		25[111] percentile	Median	75t11 percentile
0.10	0.008	60	60	60
0.20	0.010	60	60	60
0.30	0.082	60	60	60
0.40	0.474	30	60	60
0.50	0.906	15	25	40

10.4 Statistical Analysis Plan

All patients who received at least 1 dose of the combination therapy will be included in the intent-to-treat analysis for efficacy and safety. Demographic/clinical characteristics and safety data of the patients will be summarized using descriptive statistics such as mean, standard deviation, median and range. Response rates will be presented with 95% confidence intervals. The association between response and patient and clinical characteristics will be examined by Wilcoxon's rank sum test or Fisher's exact test. Overall survival time will be estimated using the

Kaplan-Meier method. Patients who drop out of the study will be included in the time to event data as "censored data". The two-sided log-rank test will be used to assess the differences of time to events between groups.

11.0 DATA CONFIDENTIALITY PROCEDURES:

Samples are identified by patients' unique identification number, which allows patient identification and linkage to the clinical database. Because many of these studies require clinical correlation, the medical record number (MRN) is maintained in the Oracle database. Only designated users may view data associated with patient identifiers. Other users see only a unique patient identifier. Dates ofbirth are not available to general users, this information is only available to central personnel and it is used to calculate age, as part of data that may be important to correlate with research assay results. This database is password-protected.

12.0 REFERENCES:

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