

New Chemotherapeutic Agents in Development: Vosaroxin (Voreloxin, SNS-595) by Sunesis Pharmaceuticals

A Review of Published Information of the Clinical Studies, the Proposed Phase 3 Program, the Competitive Environment in Acute Myeloid Leukemia and Commentary

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A. Abstract

Despite a recent strong emphasis in targeted therapies in cancer, there is still active development of chemotherapeutic agents that attack well-described cellular targets. The advantage of this approach is that the target is validated by decades of development and practice and that incremental improvements can provide adequate justification for funding. Sunesis Pharmaceuticals Inc., a South San Francisco-based biotechnology company, has been developing vosaroxin (formerly voreloxin or SNS-595), a topoisomerase II inhibitor, for the treatment of various solid and hematological cancers. In the early phases of development the company tested the compound in advanced lung and ovarian cancer and in relapsed/refractory acute myeloid leukemia (AML). Sunesis is currently planning to begin a Phase 3 study in relapsed/refractory AML in the 2nd half of 2010. During the period of development of vosaroxin (the latter part of this decade), the share price of the company has steadily declined. This report attempts to define if the current value of the stock accurately reflects a company which is set to enter the pivotal phase of development with its lead compound in an indication that, so far, lacks a definitive treatment choice. In the pursuit of an answer to this question, this report examines the development process of vosaroxin by Sunesis, the design of the proposed Phase 3 study, the state of the art in the treatment of AML and ongoing research in this malignancy by other biotech or pharmaceutical companies. The combined information may provide some answer regarding the market sentiment and assess if this sentiment is truly indicative of results thus far, the effectiveness and thoroughness of past performance and the likelihood of success in the future. In a departure from similar efforts, this paper delves in the science and clinical studies of the cancers that comprised the targets of development for vosaroxin.

B. Introduction

Certain news items in the biotech industry occasionally attract one's attention. The NASDAQ's delisting notice to [Sunesis Pharmaceuticals](#) (SNSS), a company based in South San Francisco, California, was such news. The disappointing performance of the stock of this company provided the impetus to investigate the evolution of Sunesis and the development its lead drug, vosaroxin.

Sunesis Pharmaceuticals is a typical representative of the small biotech/specialty pharma concerns that have arisen in the Bay Area in the last quarter of the 20th century. These companies came to existence by venture funding on the basis of a platform technology they viewed as "revolutionary" or "ground breaking." When

venture capital started running dry, these companies became public with promises of breakthroughs in drug discovery and the relatively speedy development and approval of their key compounds, mostly in partnership with major pharmaceutical companies. These promises have materialized only in a minority of cases. This should not have been unexpected because the development of new drugs and biologics is an exercise fraught with surprises, delays, difficult to anticipate obstacles and changes in direction. The originally raised public capital is certainly never adequate to maintain the full program envisioned by these companies; research agreements and out-licensing deals come and go raising only small amounts of money. The progressive depletion of funds forces these small biotechs to “gain focus” and concentrate on the development of a single compound, sometimes the one that is simply in a more advanced stage of development. In the meantime, the stock price enters into a continuous downwards trend, making additional financing deals more difficult to arrange without excessive dilution for existing stockholders. Companies can escape this torturous path by finally running a successful pivotal program, obtaining approval and being purchased by larger biotechnology or pharmaceutical companies.

Sunesis has definitely been on this treadmill for some time. The company was founded in 1998 with venture capital to exploit its “tethering” technology, a method of supposedly discovering promising lead compounds for difficult targets, compounds that high throughput screening was unable to identify, at least according to the company’s original claims. Nothing much has come of this



Figure 1: Sunesis’ stock performance over the last 5 years

technology; the company’s currently leading drug, **vosaroxin** (formerly voreloxin or SNS-595) is a compound in-licensed from Dainippon in 2004, a likely opportunistic acquisition to bolster the company’s flagging pipeline.

Sunesis went public in September 2005 at a price of \$6.50 per share (The IPO netted approximately \$42 million). During the ensuing years, the company wound down most of the discovery efforts with its core technology to concentrate on the clinical

development of vosaroxin. It has not structured a co-development deal on this drug with any major biotech or pharmaceutical company and it currently bears the full cost of development. The stock currently trades below \$1.00, although the board has the capacity of affecting a reverse split. The company announced the final insertion of \$28.0 million of tranche financing and it claims that it is fully financed to pursue the single Phase 3 study in recurrent/refractory AML with their lead compound, vosaroxin.

There is nothing particularly earth-shattering about the Sunesis story thus far. Its woes occur with some regularity in the world of biotech. It is important to define the reasons for which Sunesis found itself at this stage. Why is this company not perceived by investors to be as valuable as other similar companies in the oncology area with potential oncology agents near the end of the Phase 2 stage and no marketed compounds? Is the market's assessment justified or not? Do valuations reflect the market's belief in ultimate success or are concerns more ephemeral than this?

It is important to note that the data contained in this document are based solely on public releases, other publicly available information (e.g., company presentations, abstracts of scientific meetings), published peer-reviewed papers and filings to the SEC.

C. Vosaroxin: Sunesis' main drug under development

Of course, the basis of evaluating a company such as Sunesis entails examining carefully the development of its leading drugs. In this case, the main (and in reality, only) effort is focused on vosaroxin.

1. Vosaroxin chemical structure and mode of action

Vosaroxin is a naphthyridine analog, a class of compounds not previously used in cancer treatment. However, despite the "first-in-class" claims of Sunesis -which are correct as far as the chemical structure of the compound goes-, its mode of action is not. The compound is directed towards a well-known target from the early days of chemotherapy, topoisomerase II, an

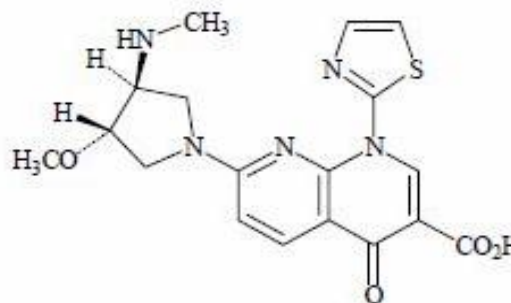


Figure 2: The structure of vosaroxin

enzyme involved in DNA replication.

Its basic mode of action is based on its capability to intercalate DNA; it inserts itself between two base pairs and these base pairs, above and below the point of intercalation, buckle, thus distorting the structure of the DNA molecule. The resulting structure abnormality prevents DNA association with a number of enzymes that are involved in DNA synthesis and replication, mainly topoisomerase II.* Inhibitors of topoisomerase II arrest mammalian cells before mitosis in the G2 phase of the cell cycle, but also produce DNA damage, which causes arrest through established cellular checkpoint controls.

As topoisomerase II has been a well characterized target, there is a number of DNA intercalating compounds that have been used for some time now in cancer treatment. Doxorubicin and daunorubicin are the best known of these. These compounds are used in the treatment of leukemias and lymphomas but also in a variety of solid tumors.

What are then the advantages of vosaroxin when compared to these other well-known and characterized drugs? Sunesis claims that vosaroxin's different chemical structure provides specific advantages such as avoidance of the multidrug resistance mechanism mediated by p-glycoprotein. P-glycoprotein (or Pgp) is a transport cell membrane protein that reduces drugs inside cells by re-exporting them across the cell membrane. A variety of mechanisms have been suggested as to how Pgp achieves this feat.^{1,2} Doxorubicin and similar agents are anthracyclines, which are recognized as substrates by Pgp and, thus, subject to removal from cytoplasm by this mechanism. It should be noted that although vosaroxin may be immune to the Pgp-mediated drug resistance, other drug resistance mechanisms and pathways do exist^{3,4} and vosaroxin is likely affected by them.

Sunesis also claims that vosaroxin-induced apoptosis can proceed by p53-independent mechanisms. P53 is a protein that induces apoptosis in normal cells when there are a number of chromosome aberrations. However, in a variety of tumor cells, p53 expression does not occur upon DNA damage and this may lead to drug resistance. Obviously, inducing apoptosis in the absence of p53 is an

* Topoisomerases are essential for the correct functioning of living cells. They maintain the correct DNA arrangement during replication and chromosome. They achieve this goal by cleaving and then reconnecting the breaks of single or double-stranded DNA as chromosomes are assembled and disassembled. Topoisomerase II, which works on double stranded DNA, is found in eukaryotic cells.

advantage, but one should consider that a variety of intercalators, such as doxorubicin, can also induce apoptosis by p53- independent pathways, a variety of which exist in malignant cells.⁵

In addition to these claims, Sunesis asserts that vosaroxin is likely less cardiotoxic than currently utilized topoisomerase II inhibitors. Cardiotoxicity is pronounced in anthracycline-based topoisomerase II inhibitors such as doxorubicin and daunorubicin.⁶ Although there is no definitively identified mechanism, most researchers believe that cardiotoxicity is caused by the generation of reactive-oxygen species (ROS) by these compounds.⁷ Sunesis claims that the chemical structure of vosaroxin is less prone to generating ROS than those of the anthracyclines.

2. Clinical studies with Vosaroxin

Sunesis started the clinical development of vosaroxin in 2005. The company performed a Phase 1 program in patients with either solid tumors or hematologic malignancies to define the safety, tolerability and pharmacokinetics of vosaroxin.

Sunesis then proceeded into Phase 2 studies in lung carcinoma. In this setting, the efficacy of vosaroxin was investigated in recurrent and refractory small and non-small cell lung carcinomas. Phase 2 studies were also initiated in platinum-resistant ovarian cancer, newly diagnosed acute myeloid leukemia (AML) in the elderly and relapsed/refractory AML in all ages. Currently, the emphasis appears to be in relapsed/refractory AML and the company has announced that it plans to begin a Phase 3 study in this indication in the 2nd half of 2010. The early clinical development of vosaroxin is discussed in detail below.

a. Phase 1 Studies with Vosaroxin

Two studies, SPO-0001 and SPO-0002 comprised the Phase 1 program of vosaroxin in solid tumors.⁸ These were typical open-label, dose escalation studies aimed to determine the maximum tolerable dose (MTD). The patients enrolled in these studies were over the age of 18 and were diagnosed with a variety of relapsed or refractory solid tumors. Ovarian, lung, colon, renal and melanoma cancers predominated.

The company enrolled "heavily pretreated" patients in the SPO-0001 (n = 43) study and "minimally pretreated"[†] to the SPO-0002 (n = 21) study. Eight dosing cohorts were utilized in SPO-0001 from 3 to 75 mg/m² on day 1 of a 21-day cycle. Because of a high rate of dose limiting toxicities at 60 and 75 mg/m², the 48 mg/m² dose was declared as the MTD for "heavily pretreated" patients. In SPO-0002, there were six dosing cohorts from 3 to 24 mg/m² administered on days 1, 8 and 15 of 28-day cycle. Because of the high rate of dose limiting toxicities at 18 mg/m², the 15 mg/m² was declared as the MTD for "minimally pretreated" patients. It should be noted that in these studies, the enrolled patients were allowed to receive up to six cycles of treatment.

The study also defined the pharmacokinetics of vosaroxin.⁸ AUC (the area under the plasma concentration-time curve) exhibited a linear relationship to the dose. Maximum concentration for the drug (C_{max}) was recorded immediately post administration. The vosaroxin concentration in plasma declined in a rather typical biphasic mode exhibiting a terminal half-life of 22 ± 11 hours. The clearance, volume of distribution at steady state (V_{ss}) and terminal half-life were independent of dose. The most prevalent dose-limiting toxicities in either study were febrile neutropenia and pneumonia.

A Phase 1 study in relapsed or refractory leukemias was performed to examine primarily the safety and pharmacokinetics of vosaroxin in hematologic malignancies and to obtain limited data for efficacy in this clinical setting. Eligible patients must have been diagnosed with a relapsed or refractory leukemia for which no standard treatment held the promise of remission. The patients were to receive up to 4 cycles of treatment. Each cycle was probably 2 to 3- weeks long. Two dosing regimens were investigated in this study. A weekly regimen in which vosaroxin was administered at the beginning of each week at a dose ranging from 10 to 90 mg/m² and a twice weekly one in which vosaroxin was administered every three days at a dose of 10 to 40 mg/m² (?)[‡]. Seventy-three patients were

[†] The term "minimally pretreated" is actually a misnomer in this situation. According to the publication that summarizes the results of these studies, a "minimally pretreated" patient was one that did not meet the definition of a "heavily pretreated". A patient was defined as heavily pretreated, if he met any of the following criteria: ≥ 6 courses of alkylator-containing treatment ; > 2 courses of carboplatinor mitomycin-C; any regimen containing nitrosourea ; radiation ≥ 25% of bone marrow area ; extensive bone metastases.

[‡] The actual dose schedule in the biweekly treatment regimen is difficult to decode from the available information

treated in this study. Although the study was open to all refractory leukemias, 84% of patients were diagnosed with acute myeloid leukemia (AML). The majority of these (78%) had refractory AML. The safety data were not surprising and within the safety spectrum seen in solid tumors. The primary grade 3 and 4 adverse experience was febrile neutropenia (40% of patients) followed by pneumonia (16%), stomatitis (14%) and sepsis (14%). The dose limiting toxicity was mostly grade 3 and 4 oral mucositis. This study defined the MTD at a weekly dose of 72 mg/m². There was an efficacy signal in this study. Of the 73 patients enrolled, 6 achieved complete remissions (CR)[§] that lasted from <1 to 7 months.

A phase 1 study in acute myeloid leukemia (AML) was also performed as part of a combined phase 1b/2 study (SPO-0012) in this indication. The phase 1 part of the study was a non-randomized, open label, dose escalation study in patients with relapsed or refractory AML. Vosaroxin was administered on day 1 and 4 of a weekly cycle at a dose of 10 to 50 mg/m² in conjunction with cytarabine.** Cytarabine was given by continuous infusion daily for 5 days at a daily dose of 400 mg/m² although, on occasions, it was also administered via bolus infusion for the same period (5 days) at a daily dose of 1g/m². Seventeen patients were treated in the phase 1 section of this study. No dose limiting toxicities were detected for the dose range tested. In terms of efficacy, 5 patients achieved complete remissions (CR) lasting from 2 to 7 months.

b. Phase 2 studies in recurrent small and non-small cell lung carcinoma

The company performed two Phase 2 studies in lung cancer. Both were open-label, single-arm, non-randomized, 2-stage clinical trials based on the Fleming algorithm for progression, rejection and acceptance of the experimental treatment.⁹ The main efficacy endpoint was objective response utilizing the RECIST criteria.¹⁰ The dose utilized in these studies was the MTD for "heavily pretreated" patients defined in the phase 1 program (48 mg/m² once every three weeks). The patients could have been treated for up to 8 cycles.

[§] It should be pointed out that in the studies reported by Sunesis, CR in AML is a combination of CR, CRp and CRi. CRp and CRi are full morphological remissions that do not meet the full definition of CR in terms of platelet and absolute neutrophil counts.

** Cytarabine (cytosine arabinoside, Ara-C) is a chemotherapeutic agent utilized primarily in the treatment of certain leukemias (AML, ALL) and lymphomas.

One of the studies enrolled 53 patients with recurrent small-cell lung carcinoma (SCLC). The study included two strata; patients were characterized as either "sensitive" or "refractory" based on the timing of the relapse (<90 or >90 days, respectively, since the last treatment). Twenty patients from each stratum were enrolled in stage 1. The criteria for progression to the 2nd stage required 2 responses in the "sensitive" stratum and 1 response in the "refractory" one. The study did progress to stage 2, although it is not clear that the refractory arm met the progression criteria. In this stage, an additional 20 patients in each stratum were supposed to be enrolled. There is no indication that the full anticipated enrollment of stage 2 was achieved. In ECCO^{††} 2007, an update on this study was presented. Overall, 28 "sensitive" and 25 "refractory" patients had been enrolled and the time of finalization of the poster presentation. Data for 22 of 28 "sensitive" and 23 of 25 "refractory" patients were presented. Overall, results were rather poor. In the "sensitive" stratum, 2 patients showed a partial response, 16 had stable disease and 4 progressed. In the "refractory" stratum, there were no responses to treatment; 5 patients had stable disease and 18 progressed.

The overall response was no better in refractory non-small cell lung carcinoma (NSCLC). In stage 1 of this study, 25 patients were to be enrolled. The criterion for progressing to the 2nd stage was 1 full/partial response. Again, there is no indication in that enrollment was completed in stage 2. As with SCLC study, an update was presented in ECCO 2007. In that update, data for 28 of 31 enrolled subjects were included. Only 1 subject met the full RECIST criteria for partial response. Twelve patients progressed and fifteen had stable disease at the time of assessment.

None of these studies met their endpoints. The study in SCLC was powered to detect a rate of objective response of 18% (7/40) in the "refractory stratum" and 30% in the "sensitive" stratum (12/40). The NSCLC was powered to detect a rate of 15% in objective response (7/50 patients). Thus, in none of these studies did the experimental treatment meet the criteria for further development.

Safety findings did not vary substantially from those of the Phase 1 studies. Neutropenia was the primary dose limiting toxicity; neutropenia of grade 3

^{††} European Cancer Organization

or higher was observed in 34% of the patients. In addition, other frequent adverse events of toxicity grade ≥ 3 included fatigue, pneumonia and arthralgia.

Overall, the decision of the company to discontinue its efforts in lung carcinoma was appropriate in view of the data. Objective response in these studies fell below the mediocre results achieved with docetaxel and pemetrexed in recurrent NSCLC.^{11,12} and well below the results obtained with topotecan, (a topoisomerase I inhibitor) in recurrent SCLC.¹³

One may question the decision to proceed with the studies in recurrent SCLC as designed, since a topoisomerase I inhibitor, topotecan, appears to have superior efficacy in that clinical setting to a topoisomerase II inhibitor, doxorubicin, even when the latter was used in combination with vincristine and cyclophosphamide (CAV regimen).¹³ Since the efficacy of topotecan was well known at the time of the design of these studies, performing a randomized, controlled study versus topotecan would have been desirable. In such a randomized study, it would have been interesting to compare the efficacy of topotecan against vosaroxin -as a single agent- and vosaroxin as replacement for doxorubicin^{##} in the CAV regimen.

c. Phase 2 Study in Platinum Resistant Ovarian Cancer

Sunesis has provided information on the progress in this study in posters in the 2008 and 2009 ASCO (American Society of Clinical Oncology) meetings. The study and preliminary results were presented in 2008 and a follow-up was summarized in 2009. Final results of this study were presented in the 2010 ASCO. It should be pointed out that the information on the design of the study was not thorough in the presentations and posters. Thus, a number of deductions on the author's part rests on incomplete information.

The study (SPO-0010) appears to have been a single-arm, non-randomized, uncontrolled, dose-escalation clinical trial. Eligible patients were diagnosed with ovarian cancer and must have relapsed or progressed within 6 months of platinum therapy (the usual definition for for platinum-resistant ovarian cancer). The patients may have had up to three previous platinum-based treatments and an additional non-platinum cytotoxic treatment. In total, 143

^{##} The typical dose for doxorubicin in CAV is 45 mg/m² and it is similar to the dose of vosaroxin of 48 mg/m² used in the SCLC and NSCLC.

patients were enrolled in the study in three consecutive dosing cohorts: The cohorts consisted of: (a) 48 mg/m² every three weeks (n = 69); (b) 60 mg/m² every four weeks (n = 39); and (c) 75 mg/m² every four weeks (n= 35) The number of planned cycles or treatment period was not included in the presentation but a number of patients (approximately 10% of the total) were apparently treated for a lengthy period of time (approximately a year) with treatment cycles of 3 to 4 weeks in duration. The GOG_RECIST^{§§} criteria were used to assess objective response.

The objective response rates observed during the study were not spectacular, but they usually are not in this disease. They ranged from 9% in cohort C and 11% in cohorts A and B. There were only 2 complete responders: 1 in cohort A and 1 in cohort B. The remainders were only partial responses. On the other hand, 18% of patients in cohort A, 30% in cohort B and 37% in cohort C had stable disease lasting ≥ 24 months. Median progression-free survival (PFS) was 83 days in cohort A, 85 in cohort B and 110 days in cohort C. For patients who had relapsed after prior Doxil^{®***} treatment (n= 44), results were very much in line with the rest with objective response at 9%, median PFS at 91 days and 32% of patients with stable disease ≥ 24 weeks.

Sunesis reported that non-hematological toxicity was rather mild in the study, with the plurality of adverse events reported at toxicity grade 1 or 2. Neutropenia, febrile neutropenia and anemia were the most common grade 3 toxicities Neutropenia (febrile or not) was more pronounced in cohort C (51% of patients) than in cohort B (16%) or cohort A (22%); Febrile neutropenia also recorded a substantial increase in cohort C (29%) while being rather infrequent in cohorts A (9%) and B (5%)

Comments: the company has pronounced that the dose of cohort B (60 mg/m² every 4 weeks) is the preferred dose for further studies mostly based on the safety profile.

d. Phase 2 Clinical Study in Acute Myeloid Leukemia

Sunesis performed two Phase 2 studies in AML: a study in newly diagnosed elderly patients who were treated with only with vosaroxin and a study in

^{§§} For brief discussion of the RECIST criteria, see Section D.2.a in [“Why do so many Phase 3 Clinical Trials Fail?”](#)

^{***} Doxil is a liposome encapsulated version of doxorubicin approved for the treatment of platinum-resistant ovarian cancer. Doxorubicin is a topoisomerase II inhibitor, very much as vosaroxin.

relapsed/recurrent AML patients in which vosaroxin was administered in combination with cytarabine.

The Phase 2 study in elderly AML patients receiving their first treatment (SPO-0014 or REVEAL-1) was mostly a dose -ranging study. The results for this study were also announced in ASCO 2010.

Patients enrolled were previously untreated, were diagnosed with AML and were ≥ 60 years of age with certain additional risk factors including higher age (≥ 70 years), lower ECOG^{†††} status, and intermediate or unfavorable cytogenetics.

This clinical trial was designed as a non-randomized, single arm, sequential-dosing group study in which the following treatment regimens were explored: 72 mg/m² at days 1, 8 and 15; Group B: 72 mg/m² at days 1 and 8; Group C: 72 or 90 mg/mg/m² on days 1 and 4.

One hundred and seventeen patients (117) enrolled in the study. Of these 29 enrolled in Group A, 36 in Group B and 52 in Group C (which had two dose levels). The remission rate (including morphological only remissions) ranged from 25% (Group C - 90 mg/m²) to 41% (Group A). Nothing much can be deduced from the differences in remission rates between the groups since the number of patients in each group was small and the groups were unlikely to have been balanced (due to the sequential nature of the study) for remission predictive factors.

The safety findings followed the pattern of the Phase 1 studies and were also consistent with those of other topoisomerase II inhibitors: approximately 50% of the subjects presented with grade 3 or higher febrile neutropenia and approximately 40% were affected by sepsis/bacteremia. Other grade 3 or higher toxicities noted in a substantial number of patients (>10%) included pneumonia, oral mucositis, other infections, fatigue, anorexia, hyperkalemia and others.

The company's justification for targeting untreated patients was that the elderly group of patients selected for the study was unlikely to benefit from conventional treatments. To its credit, in its ASCO 2010 presentation, the company clearly stated that this is no longer true, on the basis of recently

^{†††} Eastern Cooperative Oncology Group performance status: This is an ordinal scale from 0 (healthy) to 5 (dead) that describes the range of the physical capabilities of a given subject.

published results. In fact, Löwenberg *et al.* published in 2009 an extensive study (n = 813) in which elderly patients treated with a combination of cytarabine and daunorubicin recorded complete remission rates from 54% to 64% (depending on daunorubicin dosing).¹⁴

The 2nd and most important Phase 2 study explored the safety and efficacy of vosaroxin in combination with cytarabine in relapsed or refractory AML. The results of this study constitute the underpinnings of Sunesis' proposed Phase 3 program in AML.

This study included a Phase 1 component which we have already discussed in Section. Final data for the Phase 2 part of this study were announced at the 2010 ASCO meeting.

Two types of AML patients were enrolled in this open-label, uncontrolled and non-randomized study: "first relapse", patients who relapsed after achieving remission 3 to 24 months after receiving their first treatment; and "refractory", patients who never achieved complete remission or relapsed in less than 3 months after their treatment.

Two types of treatment were given in the study: The patients in the study received either 80 or 90 mg/m² on days 1 and 4 of a treatment cycle. The patients also received cytarabine on days 1 through 5 either at 400 mg/m²/days by continuous infusion or 1g/m²/day by a 2-hour bolus infusion. The decision by Sunesis to include in this study an intermediate rather than a high-dose cytarabine (a more often utilized treatment modality) was not explained. It may have been based on the belief that the efficacy of vosaroxin would compensate for the lower dose and that the tested combination would present lower than typical toxicity.

In total, 69 patients were enrolled (33 "first relapse" and 36 refractory). Overall survival in the study was 7.1 months. The remission rate was 29% (20 of 69) and the majority of the remissions were complete remissions (17/20).^{##}

The safety findings were in line with the previously established safety profile of both vosaroxin and cytarabine. The most common grade 3 or higher toxicity was febrile neutropenia (43% of subjects) followed by sepsis/bacteremia (27%) and other infections (12%). Notably, 15% of patients

^{##} The remaining three were morphological only remissions that did not meet the full remission description in terms of platelet and neutrophil counts

presented with grade 3 or higher oral mucositis. The remission rates achieved in this study hide certain discontinuities that are worth noting. The rate of remission was much higher in AML patients that have relapsed after >12 months following their first treatment (69%). For patients that relapsed between 3-12 months after the original treatment, the remission rate was only 17% and a similar number 21% was recorded for refractory patients. Of course, this has been a small study and the remission rates may change with a larger sample size. It should be noted however, that AML patients, relapsing after a considerable interval following initial treatment (>12 months), can be treated successfully with their original treatment.

Overall, the remission rate and overall survival of this limited study are in the general area of what has been achieved with well-described combination chemotherapy regimens. It is inappropriate to dwell on actual comparisons of the results of mostly Phase 2 studies. Comparison across these underpowered studies is invalid. Only an adequately powered and randomized study can produce a definitive answer. In the next session, we would be discussing Sunesis' approach to providing such an answer.

3. Vosaroxin's Phase 3 Program in Acute Myeloid Leukemia

Sunesis announced that it would be proceeding with a Phase 3 study of vosaroxin in relapsed or refractory AML in the 2nd half of 2010. Below, we will examine the company's proposed design of the clinical study and the potential problem this program may be facing when contrasted to existing or newly emergent rrAML treatments.

a. The proposed design of the Phase 3 clinical study

The company provided a brief outline of its proposed Phase 3 program. The program appears to consist of a single, multicenter, randomized and controlled clinical study in patients with recurrent or refractory AML. The study follows a group-sequential/sample size re-estimation (SSR) design, enrolling 450 subjects to detect a 40% increase in overall survival with 90% power. There is a planned interim analysis by an independent data and safety board (DSMB) which would allow for a sample size increase if warranted. A cap of 225 subjects appears to have been placed to the sample increase. The patients would be randomized into two groups both receiving cytarabine at 1 mg/m² for 5 days. In addition to cytarabine, one of the groups would receive vosaroxin at 90 mg/m² on days 1 and 4 of each cycle whereas

the other would receive placebo. There would be an induction treatment of up to 2 cycles followed by a consolidation period again of up to two cycles in the absence of progressive disease.

b. Comments on the design

The company has stated that the state of the art in the treatment of rrAML has not changed in the last 40 years. This statement obscures the fact that there has been a good number of studies in the treatment of this stage of the disease, and substantial information has been added on the efficacy and safety of a variety of regimens and certain new agents. It would be fair to say that the state of the art is certainly in evolution and has moved decisively towards treatments combining a number of anti-neoplastic agents since the 1990's, although none of these regimens has emerged as the primary choice of treating physicians and none provides overall survival outcomes that can be described as satisfactory.¹⁵ Thus, the challenge for Sunesis is substantial, especially when its agent is addressing a target (topoisomerase II) included in existing chemotherapy regimens. The potential criticisms with such a design revolve around the decision (a) to limit the control treatment to intermediate-dose cytarabine and (b) the choice of the primary endpoint and the effect of this decision on the possibility of achieving the announced statistically significant difference.

Intermediate-dose cytarabine (IDAC) as the only treatment of the placebo control group

In justifying treatment in the control group, Sunesis has stated that many patients are treated with cytarabine alone. Again, it is not clear what evidence Sunesis has that supports this statement. Certain patients may indeed receive only cytarabine, but in this case the treatment is based mostly on the high dose of this agent (HDAC), especially when it is the only drug utilized. The high dose is usually defined as 2-3 g/m² every 12 hours for 3 to 7 days. Sunesis' choice of 1 g/m² daily for 5 days (the only treatment in the control group) falls within the range of intermediate cytarabine doses (IDAC), definitely not a common treatment when cytarabine is used as a single agent to treat rrAML. In fact, even in newly diagnosed AML, high dose cytarabine in combination with a number of approved topoisomerase II inhibitors (daunorubicin, etoposide) presents a number of advantages over lower doses.¹⁶

Whatever may have been the data behind the company's preference for this control group, it would most likely make accession in the study a difficult proposition as the patients may perceive that the control arm does not provide a state-of-the-art treatment for their condition. Although enrollment shortfall connected with the adequacy of treatment of the control arm can be overcome by enrolling a substantial percentage of patients outside the US and Europe (in India, for example), it may be an "ethical" consideration that the company should carefully consider.

What would also present a problem in accessing patients for this study is the growing number of treatment regimens some of which have been shown to achieve remission rates in excess of those shown in the Sunesis clinical program. Of course, comparisons across studies are not appropriate and it should be stressed here that most of the studies with combination regimens have been relatively small, with sample sizes in the neighborhood of those already performed by Sunesis.

Overall, it would be fair to say that state of the art resides with combination regimens;¹⁷ most of these combine high (HDAC) or intermediate dose (IDAC) cytarabine with one or more topoisomerase II inhibitors such as mitoxantrone, daunorubicin and etoposide. In addition to providing relatively high remission rates, certain combinations also manage to lower the toxicities associated with the high-dose cytarabine treatments. For example, a number of small studies with the cytarabine plus mitoxantrone (HAM) as early as the 1980's showed complete remission rates in 53 to 62.5% of treated patients.^{18,19} The addition of a second topoisomerase II inhibitor, etoposide, to mitoxantrone and to intermediate dose cytarabine (the MEC regimen) also showed complete remission rates of 55%.²⁰ The inclusion of the anti-multidrug resistance agent valspodar^{§§§} into this regimen had no impact on the efficacy.²¹ This observation is quite interesting because valspodar inhibits Pgp, the same multi-drug efflux pump that vosaroxin is supposedly evading. Apparently, other multidrug resistance factors are in play here. Of course, resistance to cytarabine is the core issue here affecting treatment, with a number of new mechanisms recently discovered such as deamination of cytarabine by cytidine deaminase, an enzyme overexpressed in leukemic hematopoietic cells.²²

§§§ Valspodar is a cyclosporine-A analog that inhibits P-glycoprotein, an efflux pump that removes noxious drugs from cells. Its inhibition allows the drugs to remain within the cell and cause apoptosis

High-dose cytarabine has also been combined with purine nucleoside analogs such as cladribine²³ and fludarabine.²⁴ These purine analogs also affect DNA synthesis by inhibiting ribonucleotide reductase and DNA polymerase. The most common regimens, utilizing these purine analogs in association with cytarabine, CLAG and FLAG, also include granulocyte colony stimulating factor (G-CSF, filgrastim).

There is conflicting information regarding the agents that are best in combination with cytarabine. Milligan *et al.*²⁵ in a 405-patient study in rrAML found that the fludarabine plus cytarabine (FLA regimen) resulted in lower overall survival than cytarabine plus daunorubicin and etoposide (ADE). The same authors also detected no discernible benefits for the inclusion of G-CSF in the FLA regimen. On the other hand, George *et al.*²⁶ reported that a retrospective analysis of 162 patients, well matched for demographics and predictive factors and treated either with the GLAC-M or the MEC regimens, showed that the purine-analog regimen (GLAG) was better than the topoisomerase II-inhibitor regimen (MEC: mitoxantrone, etoposide, cytarabine) in both complete remission rates and overall survival. In addition, the incorporation of a topoisomerase inhibitor, mitoxantrone, may have provided some added benefits to the purine analog regimens (CLAG-M).²⁷

The treatment community, and potentially the regulators, may not place too much emphasis on a study comparing vosaroxin plus intermediate-dose cytarabine to intermediate-dose cytarabine alone, simply because high-dose cytarabine and the combination regimens represent the state of the art (although it is fair to say that data obtained by these regimens have not been confirmed by vigorous Phase 3 studies). Thus, comparing against the most successful or popular of the combination regimens, or, at least, against high-dose cytarabine alone, may be a better strategy in gaining both approval and market acceptance.

Overall survival as the primary endpoint and probability of success

The primary endpoint for the proposed study is overall survival. It is an appropriate choice, as utilizing other measures, such as progression-free survival (PFS) (or disease -free survival) is open to many challenges, as the recent review of the clinical studies of Avastin® in metastatic breast cancer indicate. On the other hand, the FDA has repeatedly, in this decade, approved agents in AML based on complete remission (CR) rates and

duration of remission. However, the agency is unlikely to object to overall survival as the primary endpoint, as it is a more meaningful clinical benefit endpoint than remission rates. Is it likely, however, that a combination of intermediate-dose cytarabine plus vosaroxin would produce a statistically significant increase in overall survival of approximately 30 to 40% over intermediate-dose cytarabine alone?

In the variety of Phase 3 studies that explored combination regimens and new agents in the treatment of AML, it was far more common to achieve statistically significant changes in complete remission rates between the control and the treatment arm than in overall survival. The company did not provide adequate details regarding the assumptions on estimates and variance of overall survival for its control arm so it is difficult to provide a more specific assessment.

It is exceedingly difficult to find published data of studies in rrAML utilizing only intermediate-dose cytarabine (IDAC). The studies with high-dose cytarabine may provide some guidance. A clinical study of high-dose cytarabine (HDAC) versus HDAC plus etoposide (a topoisomerase II inhibitor like vosaroxin) in 133 patients with rrAML resulted in no statistically significant differences for the total study population in overall survival despite the fact that overall survival with just HDAC (3 g/m² every 12 hours for 6 days) was 29% lower than the one recorded for HDAC plus etoposide (3.7 months versus 5.2 months, respectively).²⁸ Apparently, the variance in overall survival within each of the two groups in this limited study was high enough to prevent the mean difference from reaching significance. Such variance can somehow be minimized in smaller studies by careful stratification according to demographic and outcome prognostic factors. In a larger Phase 3 study, randomization alone should be adequate.

A similar study in 162 patients with rrAML comparing HDAC (3 g/m² every 12 hours for 6 days) to HDAC plus mitoxantrone (another topoisomerase II inhibitor) also did not result in any statistically significant differences in overall survival.²⁹ In this case, the combination of high-dose cytarabine and mitoxantrone achieved a lower median overall survival estimate than high-dose cytarabine alone (8 months versus 6 months, respectively).

Some interesting information regarding the performance of an intermediate-dose cytarabine in relapsed AML can be obtained from the Phase 3 study that Vion Pharmaceuticals performed in this particular indication with

laromustine (VNP40101M, Onrigin®).³⁰ This study is discussed in greater detail in [Section 4](#) (A brief overview of the competitive landscape in AML). Vion described the cytarabine dose used in its trial as “high”, although it does not meet the definition. The dose was 1.5 mg/m² daily for only three days. Thus, the overall cytarabine dosing in the laromustine study was somewhat lower than in the proposed Phase 3 design by Sunesis (4.5 g vs 5.0 g). The cytarabine + placebo arm (n = 86) in that study showed complete plus morphological remission rate of 19% and a median overall survival of 5.9 months with 95% confidence interval of 4.6 to 9 months.

It should be noted that the Sunesis Phase 2 study in rrAML (intermediate-dose cytarabine + vosaroxin) recorded a median OS at the same range as the aforementioned studies: approximately 7.1 months with the 95% confidence interval being quite broad (2 – 11 months).

Assuming that intermediate-dose cytarabine alone would not perform as well as high-dose cytarabine in rrAML, utilizing the intermediate dose in the cytarabine-only arm in the planned Phase 3 study may provide Sunesis with the chance in obtaining the significant difference it seeks in overall survival, assuming that the variance is not unusually large. The assessment of this approach by regulatory agencies and by the treatment community is, at best, uncertain.

4. A Brief Overview of the Competitive Landscape in AML

Because outcomes in AML have not drastically improved over the last few decades, it is an active development area. In fact, the field may be regarded as “crowded” when one considers the size of the market. Below, there is a brief overview of the major groups of new and existing drugs. The overview is not meant to be an exhaustive survey of clinical development in AML. It only serves to provide a framework for the environment in which vosaroxin may be launching -if it does- in the US in the next decade.

Sunesis does have a few direct and a number of “indirect” competitors. Vosaroxin is not the only hopeful in the race to provide new choices in topoisomerase II inhibitors. Antisoma plc is developing another novel topoisomerase II inhibitor, amonafide (or AS1413). The company is making claims similar to Sunesis' for its compound in terms of avoidance of multidrug and apoptosis resistance mechanisms. However, instead of addressing relapsed/refractory AML which is a recognized subtype of AML, Antisoma has

targeted "secondary acute myeloid leukemia". According to Antisoma, this category includes patients who have progressed to AML from myelodysplastic syndromes (MDS) or as a result of treatment for another malignancy. These patients have poor prognosis but it is questionable if they can be placed in a separate category from others patients with poor prognosis factors based simply on cytogenetics or age. AS1413 is roughly the same phase of development as vosaroxin. The company announced results of its Phase 2 study with amonafide in secondary AML in ASCO 2010. The combination of standard-dose cytarabine (200 mg/m²/day by continuous IV infusion for 7 days) and 600 mg/m² amonafide for 5 days resulted in a complete remission rate of 38.6%. Median overall survival was 200 days. Antisoma is currently conducting a Phase 3 study with amonafide in secondary AML (ACCEDE). The study would access approximately 450 patients. The study design avoids some of the potential criticism of the Sunesis Phase 3 study by comparing the safety and efficacy of standard dose cytarabine (200 mg/m²/day by continuous IV infusion for 7 days) plus amonafide to those of standard-dose cytarabine plus daunorubicin (45 mg/m² for 3 days). Enrollment in this study commenced in late 2009. The primary endpoint is complete remission rate. The fly in the ointment here is that high doses of anthracyclines (e.g., daunorubicin) of about 90 mg/m² have recently been shown to be more effective in inducing remission and extend overall survival in a randomized Phase 3 study in 657 AML patients.³¹ The amonafide Phase 3 study is also not blinded, probably because of the differential schedule and mode of administration of daunorubicin and amonafide. However, the difference in duration of infusion is not dramatic and dummies plus concealment may have allowed effective blinding.

Beyond topoisomerase II inhibitors, there are a number of small molecules entering the field addressing more recently discovered targets. Among them, there is a group of inhibitors that bind to the FMS-like tyrosine kinase 3 (FLT3). This kinase is expressed on the surface of immature progenitor hematopoietic cells; mutations of this kinase have been identified in as many as 50% of AML patients.³² Novartis (PKC-412/Midostaurin and CHR-258/TKI258), Sugen (SU11248 - Sunitinib), Millenium Pharmaceuticals (MLN518 - Tandutinib), Cephalon (CEP-701 - Lestautinib), Bayer (BAY-43-9006 - Sorafenib) and Kyowa (KW-2449) are the companies currently having FLT3 inhibitors under development.^{33,34} Results so far have indicated that these compounds have low toxicity but have very moderate efficacy as single agents; effective resistance to them builds relatively quickly.³⁵ The effort is now under way to test these

inhibitors in combination with existing chemotherapy agents (high-dose cytarabine, mitoxantrone, etoposide, daunorubicin and others) as preclinical results indicate that such a combination may be quite effective assuming that the sequence of administration is appropriate.³⁴ Because the FLT3 inhibitors (at least the current group) work in association with typical chemotherapeutic regimens, they may not be direct competitors to vosaroxin. However, vosaroxin would have to be shown to work with them effectively if it intends to progressively displace existing topoisomerase II inhibitors.

The next group consists of the farnesyl transferase inhibitors. Oncogenic versions of the Ras genes, which code for proteins involved in signal transduction, have been identified in a number of patients diagnosed with AML. Their exact incidence is still uncertain (anywhere from 3% to 40%). The presence of oncogenic Ras genes (the mutant versions are essentially stuck in the "on" phase) prompted the examination of the efficacy and safety of farnesyl transferase inhibitors in AML. These inhibitors block the farnesylation (transfer of the farnesyl group, a 15-carbon isoprenoid) of Ras, and thus its transfer and incorporation in the plasma membrane. Of these inhibitors, Johnson&Johnson's tipifarnib (Zarnestra™) is the one with the more substantial presence in the AML space. The FDA refused to approve tipifarnib in 2005 for use in elderly AML patients mainly because of the lack of robustness in the clinical development program and compelling results (no increase in overall survival).³⁶ Since then, tipifarnib has been utilized in a number of studies in combination with the typical chemotherapeutic agents in AML with encouraging results.³⁷

Laromustine (Onrigin®, Vion Pharmaceuticals) has been investigated in the treatment of both newly diagnosed and relapsed/refractory AML. This is a DNA alkylating agent that creates inter-strand cross-links that are difficult to repair and lead to cell death. Earlier in this decade, a number of Phase 1 and early Phase 2 studies were performed with this alkylating agent in patients with refractory AML³⁸ and in elderly patients with newly diagnosed AML.³⁹ In these studies, laromustine at a dose of 600 mg/m² every four weeks was the sole treatment agent. Its activity in refractory AML was not substantial, but it performed better in a Phase 2 study in elderly patients with newly diagnosed AML and several adverse prognostic factors.⁴⁰ In that study, 32% of patients experienced complete or morphologic remission. Mortality was high (1-year survival was 21%) and median overall survival was low (3.2 months) but the study was uncontrolled, so it is difficult to put these numbers in an appropriate perspective. Vion Pharmaceuticals also performed a randomized, placebo-

controlled Phase 3 study of laromustine and cytarabine in relapsed AML.³⁰ This study is particularly interesting not only because of the information it provided about the potential of laromustine in relapsed AML but because of certain similarities this study possesses with the Sunesis Phase 3 design. The authors of the study identified the cytarabine dose as "high" although it does not meet that definition. All patients (n= 268) were treated with cytarabine at 1.5 g/m² for 3 days and received 600 mg/m² on day 2 of a 4-week cycle. The overall amount of cytarabine given (4.5 g/m²) is slightly lower than the one Sunesis is planning to administer in its Phase 3 study. The results were interesting as well. There was a significant difference in complete and morphological remission rates (35% in the laromustine + cytarabine arm vs. 19% for cytarabine + placebo). No statistically significant difference in overall survival was detected. The authors attributed this lack of effect on overall survival to the significantly higher rate of mortality in the laromustine + cytarabine arm. Examining the safety information of the study, it became clear that the dose of laromustine utilized was excessively myelosuppressive. Further attempts to investigate laromustine in relapsed AML may be undertaken, possibly with lower doses. The National Cancer Institute (NCI) is currently investigating the combination of laromustine, daunorubicin and cytarabine in AML patients with unfavorable cytogenetics.

Another group of agents that has received substantial attention consists of DNA demethylating agents. The main members of this group of compounds are azacitidine (Vidaza[®], Celgene) and decitabine (Dacogen[®], Eisai). They are not particularly new; they have been used in AML for some time, although their toxicity was substantial.⁴¹ These compounds were eventually approved for the treatment of myelodysplastic syndromes (MDS) but not for AML. Recently, lower doses of these compounds with lower toxicity have been utilized to treat AML in the elderly with some encouraging results (a 26% CR rate for decitabine) but the studies have been small.^{42,43} In the group of compounds that have received approval in the treatment of MDS and have certain activity in AML, one needs to include lenalidomide (Revlimid[®], Celgene), a thalidomide derivative.⁴⁴ High doses of lenalidomide can produce excellent results on occasions⁴⁵ and are under investigation by Celgene in older AML patients or in patients with certain cytogenetic characteristics.

A number of newer nucleoside analogs such as clofarabine (Clolar[®] Genzyme), troxacitabine (Troxyt[®], SGX) and sapacitabine (Cyclacel Pharmaceuticals) represent potential competitors to vosaroxin. These second generation nucleoside analogs have much better pharmacokinetic properties⁴⁶ than

cladribine and fludarabine which have been discussed in [Section 3b](#). Clofarabine in combination with intermediate-dose cytarabine (1g/m²/day for 5 days) resulted in a 60% remission rate in elderly AML patients.⁴⁷ Similar remission rates (63%) were also seen in a study of clofarabine in combination with low dose cytarabine (20 mg/m²/day for 14 days) in elderly patients diagnosed with AML or high-risk myelodysplastic syndrome (MDS).⁴⁸ A Phase 1 study in relapsed/refractory AML with clofarabine with or without cytarabine and idarubicin has been completed and a Phase 2 is ongoing.⁴⁹ Troxacitabine completed a limited Phase 1/2 study as a sole treatment in refractory AML⁵⁰ but development seems to have been lagging since. On the other hand, Cyclacel is more aggressively developing its nucleoside analog, sapacitabine. The company has concluded an early Phase 2 study in AML and MDS. The data on AML were announced during the ASH**** 2009 meeting. Sixty elderly patients (median age = 77 years) either newly diagnosed with AML (n = 51) or in first AML relapse (n = 9) and with the majority of them having intermediate or unfavorable cytogenetic predictive factors were treated solely with either 200, 300 or 400 mg b.i.d for 7 days every 3-4 weeks. The highest dose (400 mg b.i.d) achieved the best results: a 25% CR rate. Nausea and vomiting, diarrhea, anemia, neutropenia, febrile neutropenia were common adverse events. Cyclacel is investigating possible combination regimens in order to enhance the efficacy of sapacitabine.

There are, of course, a number of other agents in Phase 2 studies: CPX-351 by Celator Pharmaceuticals is a liposomal formulation of cytarabine and daunorubicin. Celator Pharmaceuticals provided a recent update of the Phase 2 study comparing CPX-351 to a typical 7-day cytarabine + 3-day daunorubicin treatment. The interim results, announced at the 2010 ASCO meeting, showed that in newly diagnosed AML patients, those treated with CPX-351 (n = 57) showed a 61.5% remission rate compared to 50% for those treated with the "7 +3" regimen.⁵¹ There is also alvocidib (Sanofi), which is a cyclin-dependent kinase (CDK) inhibitor (cyclin-dependent kinases are involved in cell cycle progression). Alvocidib is currently being evaluated for efficacy and safety in both CLL and AML. [Clinical studies of alvocidib in AML](#) include cytarabine and mitoxantrone given in combination with this kinase inhibitor. In earlier stage of development in AML -and various other cancers- there is ARRY-520 by Array Biopharma. This is a molecule that inhibits the kinesin spindle protein, an action that disrupts mitosis of actively dividing malignant cells and induces cell death.

**** American Society of Hematology

Data from a recent dose-escalation Phase 1 study indicate a certain level of activity in advanced leukemias.⁵²

The list of compounds described above illustrate the substantial level of activity in AML research and underline the extent of the challenge facing new agents such as vosaroxin.

5. Discussion and Conclusion

The Sunesis story is somewhat typical in biotech. A company formed on a platform technology that promises the faster development of new compounds is forced by the funding situation to modify its approach and develop an in-licensed compound. In the process of performing demanding and expensive clinical trials, the original technology is mothballed or out-licensed (with some justification, in the case of Sunesis).

The question here is if the compound itself merits excitement on the part of the treatment and investment community. Vosaroxin addresses a target, topoisomerase II, that has been identified some time ago and which is addressed by a number of approved compounds (doxorubicin, daunorubicin, idarubicin, mitoxantrone, etoposide, etc). These compounds have been available to the treatment community for decades, the information collected on their efficacy and safety is voluminous and there is substantial familiarity in their use. Several of these (mitoxantrone, doxorubicin, daunorubicin) have worrisome side effects such as substantial cardiotoxicity and their use may decline if a credible alternative appears.

Addressing the investment community and regulatory agencies, Sunesis should offer a compelling argument as to why vosaroxin represents a substantial (and clinically relevant) improvement over the multitude of existing topoisomerase II inhibitors and other treatment modalities. This argument should be bolstered not only by *in vitro* data, but by convincing clinical data.

Can Sunesis make any argument on the clinical data already collected? The absence of controlled, randomized studies makes this a difficult proposition. There is an ongoing, animated argument in oncology drug development, of non-randomized, single arm studies versus randomized, controlled studies. Sunesis program with vosaroxin has avoided controlled studies. Of course, randomized and controlled studies with small sample sizes are both complex (require effective stratification) and incorporate a number of statistical compromises (higher significance levels). On the other hand, non-randomized studies without

an active control (or placebo) depend highly on historical controls. If the historical control does not match the study population, or if the data are just too old (include an older standard of care), it can be very deceiving. There is no public access to the full characterization of the historical control included in the Sunesis studies for an independent evaluation of the validity of conclusions.

In addition to the problems of the Phase 2 program, the current Phase 3 study as structured would not provide an answer to the question of superiority (in safety and efficacy) of vosaroxin to existing topoisomerase II inhibitors. The comparison against only intermediate-dose cytarabine further makes Sunesis' challenge that much more difficult to overcome. Targeting a substantial difference in overall survival as the primary endpoint intensifies the difficulties, despite its desirability on clinical grounds. Not answering key questions is a pity, considering the fact that Sunesis would be spending a substantial amount of money on this study. To be effective, Sunesis should provide this answer sooner rather than later and make a strong argument as to why vosaroxin would -or should- capture a substantial part of the market from existing topoisomerase II inhibitors or other treatment modalities.

Providing a strong rationale for vosaroxin as a replacement for older topoisomerase II inhibitors is crucial as many of the newer drugs are usually ineffective as single agents and require the addition of cytarabine and/or a topoisomerase inhibitor. The lower level of cardiotoxicity, if shown clinically, would certainly help (although etoposide is also non-cardiotoxic). In conclusion, the efficacy and safety of vosaroxin needs to be evaluated directly in a clinical study which would contrast this agent against the typically utilized combination regimens of today.

D. Keywords

Vosaroxin - Voreloxin - SNS-595 - Topoisomerase II Inhibitor - Acute Myeloid Leukemia - Relapsed - Refractory - Chemotherapy - Cytarabine - Daunorubicin - Doxorubicin - Etoposide - Mitoxantrone - Combination Regimen - Amonafide - FLTK3 Inhibitor - Farnesyl Transferase Inhibitor - Laromustine - Azacitidine - Decitabine - Lenalidomide - Clofarabine - Troxacitabine - Sapacitabine - CPX-351 - Alvocidib - ARRY-520 - Phase 3 - Phase III - Phase 2 - Phase II - Phase 1 - Phase I - Clinical Trial - Clinical Trial Design - Endpoints - Cancer - Oncology -Progression-Free Survival - PFS - Overall Survival - Complete Remission

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