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EMA/462376/2017
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal Assessment report

Qinprezo (WD)

International non-proprietary name: vosaroxin

Procedure No. EMEA/H/C/004118/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADR	Adverse drug reaction
AE	Adverse event
AML	Acute myeloid leukaemia
ANC	Absolute neutrophil count
Ara CTP	Arabinosyl cytosine triphosphate
AUCinf	Area under the concentration versus time curve from time zero to infinity
BCRP	Breast cancer resistance protein
BP	British pharmacopoeia
BSA	Body surface area
CI	Confidence interval
Cmax	Observed maximum concentration
CPARR	Clinical Pathology and Response Review
CR	Complete remission
CRi	Complete remission with incomplete blood count recovery
CRp	Complete remission with incomplete platelet recovery
CTCAE	Common Terminology Criteria for Adverse Events
DEHP	Diethylhexylphthalate
ECG	Electrocardiographic
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
EMA	European Medicines Agency
ESMO	European Society of Medical Oncology
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
GMP	Good manufacturing practice
HDPE	High density polyethylene
hERG	human ether-a-go-go-related gene
HIDAC	High-dose cytarabine
HR	Hazard ratio
IC50	Concentration of drug producing 50% inhibition
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDAC	Intermediate-dose cytarabine
IWG	International Working Group
LDAC	Low dose cytarabine
LFS	Leukaemia-free survival
MedDRA	Medical Dictionary for Regulatory Activities
MRP2	multidrug resistance-associated protein 2
NLT	Not less than
NMT	Not more than
OAT1	organic anion transporter 1
OATP	organic anion transporting peptide
OCT	organic cation transporters
OS	Overall survival
PDCO	Paediatric Committee
P-gp	P-glycoprotein
Ph. Eur.	European Pharmacopoeia

PIP	Paediatric Investigational Plan
PK	Pharmacokinetic(s)
PR	Partial remission
PT	Preferred Term
PVC	Polyvinyl chloride
SAE	Serious adverse event
SmPC	Summary of Product Characteristics
SOC	System Organ Class
t1/2	Terminal half-life
TEAE	Treatment-emergent adverse event
TF	Treatment failure
UGT	Uridine diphosphate glucuronosyltransferase enzyme
USP	United States Pharmacopoeia
UV	Ultraviolet
WBC	White blood cells

1. Recommendation

Based on the review of the data and the Applicant's response to the CHMP LoQ on quality, safety, efficacy and risk management plan, the CHMP considers that the application for Qinprezo, an orphan medicinal product, in combination with cytarabine in the treatment of adult patients ≥ 60 years of age with relapsed or refractory acute myeloid leukaemia (AML), is not approvable since major objections still remain, which preclude a recommendation for marketing authorisation at the present time.

Major Objections

Though the unmet need and the considerations to argue that there may be a place for vosaroxin in the therapeutic armentarium to treat elderly patients (≥60 years) with relapsed/refractory AML are recognized, the overall B/R of Qinprezo for this indication remains currently negative for the following reasons:

- though the effect on OS between the study arms and the OS data in itself in the vosaroxin/cytarabine group, if true, can be considered clinically meaningful, there is lack of replication of the data in the context of a single (negative) pivotal trial and inconsistent results within the subgroup of patients ≥60 years not pre-specified for confirmatory testing;
- lack of efficacy and the increased toxicity in the sub-subgroup of patients ≥60 years with late relapse.

Therefore, in order to identify the patient population best treated with the vosaroxin/cytarabine combination,

1. a further substantiation of the subgroup of patients ≥60 years with relapsed/refractory AML should be provided demonstrating a robust clinically meaningful benefit. Special attention should be given to the replication of the subgroup finding.
2. the applicant is requested to provide further justification that adequate prophylaxis could improve the safety outcome and discuss the impact on OS for patients ≥60 years with late relapse.

Questions to be posed to additional experts

The CHMP agreed to seek inputs from a SAG- oncology.

Inspection issues

None

New active substance status

Based on the review of the data, the CHMP considers that the active substance, vosaroxin, contained in the medicinal product, Qinprezo, is to be qualified as a new active substance in itself.

2. Executive summary

2.1. Problem statement

AML is a disease characterized by rapid, uncontrolled proliferation of malignant clonal hematopoietic stem cells that accumulate as immature, undifferentiated cells (blasts) and lead to impaired production of normal hematopoietic elements which in turn leads to anaemia, neutropenia, and thrombocytopenia. If left untreated, AML can result in death within weeks.

The incidence of AML in Europe is approximately 5 to 8 cases per 100,000 per year among adults, with approximately 4 to 6 deaths per 100,000 per year. The number of new cases per year in Europe (EU-27) is estimated at 18,400. The 5-year survival rate is estimated to be 26%. While advances in treatment have shown increases in survival rates for acute lymphocytic leukaemia, chronic lymphocytic leukaemia, and chronic myeloid leukaemia, the same improvements have not been seen for AML.

AML is generally a disease of older people (median age of 68 years at diagnosis) and is more common in men than in women. The incidence increases sharply with age, ranging from 1.8 cases per 100,000 people aged less than 65 years to 17.6 cases per 100,000 people over 65 years. In addition, the mortality rate increases dramatically with increasing age. It has been reported 5-year survival rates of 3% to 8% in patients ≥60 years compared with rates of up to 50% for younger patients.

First line treatment

The standard treatment for newly diagnosed AML has not changed appreciably in the last several decades and chemotherapy is divided into two treatment phases: induction and consolidation. Induction chemotherapy attempts to reduce the number of leukemic cells in blood and bone marrow below levels detectable by morphologic analysis, thus achieving complete remission (CR). Once a CR has been obtained, consolidation therapy is administered with the goal of eliminating undetected residual disease, thereby reducing the risk of relapse. Following consolidation chemotherapy, further consolidation with allogeneic stem cell transplant (SCT) may improve relapse-free survival and overall survival (OS) in patients with intermediate- and poor-risk disease.

The most widely used induction regimen in patients younger than 60 years is cytarabine at 100 to 200 mg/m^2/day continuous IV infusion for 7 days in combination with an anthracycline (e.g., idarubicin or daunorubicin) for 3 days (so called “7 + 3” regimen). High-dose cytarabine (HIDAC; 2000 mg/m^2/day or more) in combination with an anthracycline is also used, particularly in younger patients, although the clinical benefit has been questioned and concerns have been raised about neurotoxicity.

As older patients may not tolerate intensive chemotherapy, recommended treatments include low-intensity therapy with low-dose cytarabine (LDAC, at e.g. 20 mg SC twice daily for 10 days per cycle) or a hypomethylating agent (e.g., 5-azacytidine or decitabine).

Currently approved therapies in the EU in the treatment of AML:

- Ceplene (histamine dihydrochloride) as maintenance therapy in combination with IL-2 for patients in first remission.
- Dacogen (decitabine) for newly diagnosed AML in patients > 65 years who are not candidates for standard induction therapy.
- Vidaza (azacitidine) for patients with AML not candidates for HSCT who are ≥ 65 years with >30% marrow blasts and patients with 20-30 % blasts and multi-lineage dysplasia.

The rate of CR after induction chemotherapy is estimated to be 50% to 70%. In younger adults, 60% to 80% of patients achieve CR with intensive induction regimens but in older adults, this CR rate decreases to 40% to 50%. Failure to achieve CR with one or two treatment courses carries a poor prognosis even if a CR is subsequently achieved with salvage therapy.

Once CR has been achieved after induction therapy, consolidation therapy is often administered to eliminate minimal residual disease and maintain the remission. For patients in first CR (CR1), allogeneic SCT is a potentially curative treatment option that results in improved relapse-free survival and offers the best opportunity for long-term survival for some patients (e.g., those with intermediate- and high-risk AML).

If no CR is achieved following intensive induction chemotherapy (typically 1 or more cycles), AML is considered to be refractory. Although there are various definitions of refractory AML, it has been generally defined as patients having either no initial CR or a first CR lasting less than 3 to 6 months.

Even when a CR is achieved with induction treatment, AML will relapse in most patients.

Second line treatment

There is no current standard of care regimen for the treatment of relapsed and refractory AML, and cytarabine alone or in combination regimens (e.g., with anthracyclines) remain the most commonly used treatment options. Patients with significant co-morbidity and the elderly are often not eligible for intensive treatment and intermediate dose cytarabine (IDAC) regimens of 0.5 to 1 g/m^2 as a 2 hour IV infusion for 5 days have been shown to be equally clinically effective but substantially less neurotoxic compared with HIDAC and generally well tolerated.

Currently there are no approved therapies in the EU specifically for the treatment of relapsed or refractory AML.

Treatment outcomes in relapsed or refractory AML vary depending on several factors. The best predictor of response to therapy in the relapsed setting is duration of the first CR after initial first line therapy (CR1): if CR1 duration < 1 year, the likelihood of a second CR is 14% whereas for those with CR1 duration > 1 year, the likelihood of a second CR is ≥40%. It has been reported that median survival of patients who relapsed within 6 months after CR1 was 1.8 months and the median survival for those who relapsed between 6 and 12 months was 5.5 months.

In the relapsed/refractory setting, the prognosis for older patients is significantly worse than that of younger patients and is often associated with poor performance status, comorbidities, unfavourable cytogenetics, and multidrug resistance. It has been reported from several randomized studies CR rates 3-23% lower in older patients with relapsed/refractory AML compared with the overall population, and a rate of 2^{nd} CR of 47% if initial CR duration was 12-24 months but a reduced 2^{nd} CR < 20% if initial CR duration was < 6 months.

In the last four decades, few advances in the chemotherapeutic treatment of relapsed/refractory AML have been made, particularly in older patients. Few randomized studies have been conducted in patients above 60 years and available evidence suggests response rates may be improved with more aggressive therapy. However, increased toxicity is a concern and no survival benefit has been observed. The only curative option for relapsed/refractory AML is allogeneic SCT, as salvage therapy or following second CR achieved with salvage chemotherapy. Rates of transplantation are lower in older than younger patients.

Outcomes with transplantation are superior when performed in second CR rather than in active first relapse or refractory disease. It has been reported a 3-year leukaemia-free survival (LFS) rate of 60%, 35%, and 25%, for transplants performed during first CR, second CR, or in active relapsed disease, respectively.

Patients who are not in remission at the time of transplantation are reported to have an OS at 3 years of 19%. Duration of first CR > 6 months, good or intermediate cytogenetics prior to transplant, absence of circulating blasts, and good performance status are favourable predictors of outcome for patients with active disease who receive allogeneic transplant. Recent improvement in donor availability and supportive care has led to a significant decrease in treatment-related morbidity/mortality, making transplantation more widely utilized than in previous decades.

2.2. About the product

Vosaroxin, a first-in-class anticancer quinolone derivative, is a DNA-intercalating topoisomerase II inhibitor. Although the mechanism of action is most similar to other topoisomerase II inhibitors (e.g. anthracyclines and anthracenediones), vosaroxin is minimally metabolized and produces no significant amount of free radicals, reactive oxygen species, DNA crosslinks or DNA alkylation that have been linked to cardiac toxicity. Vosaroxin induces G2/M arrest and S-phase lag. The S-phase lag may contribute to the synergy seen when administered in combination with cytarabine, as cytarabine is an S-phase active agent.

Vosaroxin is indicated in combination with cytarabine for the treatment of patients ≥ 60 years with relapsed or refractory AML.

Vosaroxin is administered in combination with cytarabine for up to 4 cycles, consisting of 1 or 2 induction cycles and 1 or 2 consolidation cycles. Each cycle of 28 days (subject to haematological recovery) comprises the following:

> Vosaroxin (days 1 + 4) by slow IV injection at 90 mg/m^2 for Cycle 1 and 70 mg/m^2 for all subsequent cycles
>
> +
>
> Cytarabine (days 1- 5) as 2 hour IV infusion at 1 g/m^2

Dosing is capped at a maximum BSA of 2.4 m^2

2.3. The development programme/Compliance with CHMP guidance/Scientific advice

The clinical development program includes comprehensive clinical pharmacology studies, one single placebo-controlled pivotal study (VOS-AML-301, also called VALOR) supported by 2 uncontrolled studies (phase 1b/2 SPO-0012 and phase 2 SPO-0014) in patients with AML and safety data from over 1000 patients that included 648 patients with haematological malignancies who were treated with vosaroxin. The development programme in view of the proposed indication and posology is considered acceptable.

CHMP scientific advice was provided on 20th May 2010 (EMA/CHMP/SAWP/287102/2010). CHMP agreed on the proposed pivotal phase 3 study characteristics, including choice of comparator, endpoints and study design. However, the definition of relapsed and refractory AML that was applied in the pivotal VALOR study was different from the definition presented at the SA with regards to the time period between the first day of the last induction cycle (can be 1 or 2 cycles) and the moment that relapsed or refractory disease was established. Refractory was defined as relapse < 90 days and

relapse was defined as relapse after ≥ 90 days. Relapse was further subdivided in early or late relapse, i.e. after ≥ 90 days and < 12 months, or ≥ 12 months and ≤ 24 months, respectively.

The conduct of an interim analysis was not recommended. The applicant was also advised to consider adding stratification factors with regards to likelihood of patients having subsequent haematopoietic stem cell transplant (HSCT) and with regards to cytogenetics although this advice was not followed. However the Applicant applied the following strategy: 1) the suitability of the patient for transplant was assessed by the investigator at the time of the randomisation request and 2) the cytogenetic profile was assessed as baseline, but was not a stratification factor.

CHMP protocol assistance was provided on 13th December 2012 on a paediatric clinical plan (EMA/CHMP/SAWP/769000/2012) and follow up scientific advice was given on 9th January 2013 on significant benefit of vosaroxin in relapsed/refractory acute myeloid leukaemia (AML) (EMA/CHMP/SAWP/768999/2012).

Vosaroxin received orphan designation for the treatment of acute myeloid leukaemia on 26th April 2012 (EU/3/12/990) (see section 4).

The COMP considered that the phase III VALOR study was well-designed for the purpose of documenting a clinically relevant benefit of the combination of vosaroxin and cytarabine versus placebo and cytarabine. Clear evidence of OS superiority resulting from the VALOR study would be considered sufficient to support the assumption that vosaroxin will be of significant benefit for AML patients.

No national scientific advice was provided by any MS.

2.4. General comments on compliance with GMP, GLP, GCP

Studies were conducted in compliance with GMP, GLP, and GCP.

It is stated in the dossier that studies in the clinical development program were conducted in accordance with the ICH guidance for Good Clinical Practice E6. Confirmation has been provided as a statement that the clinical trials within the submission, conducted outside the EU, meet the ethical requirements of Directive 2001/20/EC.

The only GCP inspection performed prior to submission of the marketing authorization application by Regulatory Authorities was an inspection by Health Canada, as part of pivotal study VOS-AML-301(VALOR), dated 19th August 2013. The outcome of this inspection demonstrated the site concerned had been in compliance with regulatory principles (rating C).

A routine GCP inspection was requested by CHMP on pivotal study VOS-AML-301 on 9th February 2016. No specific concerns had been identified during the initial assessment but in line with GCP Inspection Policy for centralised applications it was triggered by the indication in AML, the adaptive design of pivotal study and that no inspections had been conducted by an EU inspectorate. The inspections took place in April 2016 and the integrated GCP report is dated 1st June 2016. No critical findings were identified and the major / minor findings reported were anticipatedto be unlikely to have an impact on the quality of the data.

2.5. Type of application and other comments on the submitted dossier

- Legal basis

This application has been submitted in accordance with Article 8.3 of Directive 2001/83/EC as a new active substance, and consists of a complete dossier with administrative, quality, non-clinical and clinical data. The eligibility for a submission through the Centralised Procedure (CP) under Article 3(1)

of Regulation (EC) No 726/2004 (mandatory scope) indent 4 (orphan designated medicinal product) was confirmed by the CHMP on 20th November 2014.

- Accelerated procedure

  N/A

- Conditional approval

  N/A

- Approval under exceptional circumstances

  N/A

- Biosimilar application

  N/A

- 1 year data exclusivity

  N/A

- Significance of paediatric studies

  A positive opinion was issued by the EMA on 8th August 2014 (P/0204/2014) on PIP in AML that included performing two clinical trials (VOS-PED-101 and VOS-PED-102) in patients from one month to less than 18 years with a deferral for their initiation. A waiver was agreed for patients below 28 days of age.

  Subsequent PDCO opinion on 13th November 2015 confirmed acceptance of a change of timelines for initiation of VOS-PED-101 (December 2017) and VOS-PED-102 (March 2022) studies and their completion (December 2021 and July 2026 respectively). Final EMA decision on 4th December 2015 has confirmed the acceptance (P/0296/2015).

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

Vosaroxin is a new chemical entity, proposed in combination with cytarabine, for the treatment of adult patients (≥ 60 years of age) with relapsed or refractory acute myeloid leukaemia. The recommended dosage of vosaroxin is 90 mg/m^2 for Cycle 1 of treatment and 70 mg/m^2 for all subsequent cycles administered on Days 1 and 4 of each cycle. The maximum possible daily dose of vosaroxin is limited to 216 mg based on the specified maximum body surface area of 2.4 m^2

The drug product is presented as a vosaroxin 10 mg/ml solution for injection, with vosaroxin solubilised *in situ* as its methanesulfonate salt. The proposed packaging materials are a 25 ml amber, type I, glass vial with a stopper, flip-off cap and overseal.

The Applicant obtained scientific advice from the EMA with regard to the designation of starting materials, control of drug substance (including clinical batches), stability package for the drug substance and the drug product (including photostability), and the suitability of the drug product formulation for the paediatric population.

3.1.2. Active Substance

The proposed starting materials are well characterised and relatively simple molecules, which require a number of discrete synthetic steps interspersed with isolated intermediates, to prepare the drug substance. As a result, there is sufficient opportunity for purging impurities or synthetic by-products. Coupled with a control strategy that is generally robust, the proposed starting materials are considered to be acceptable for regulatory purposes.

Characterisation of the drug substance is generally satisfactory; and elucidation of structure and absolute configuration is confirmed. The drug substance is known to exhibit polymorphism with two anhydrous forms (I and IV) potentially arising from commercial synthesis. The drug substance is zwitterionic in aqueous solution and has poor aqueous solubility. The identification of potential impurities is comprehensive and the associated control strategy is acceptable; the drug substance itself is noted to be mutagenic and clastogenic, thus control of related substances of vosaroxin in line with general ICH guidance Q3A is accepted.

The control specification proposed for the drug substance is considered to be acceptable. Comprehensive batch analytical data have been provided, for three process validation batches and four primary stability batches that comply with the proposed specification.

The drug substance is stable to elevated temperature but is photosensitive. Thus, while a new "UV safe" secondary HDPE pack is proposed, further data are required to demonstrate that this is at least as photoprotective as that used in stability studies. A retest period of 48 months at NMT 30 ^{o}C is approvable for the drug substance.

3.1.3. Finished Medicinal Product

Vosaroxin 10 mg/ml Injection for Solution is intended for administration by slow, intravenous injection via a central line and is not intended to be administered as an admixture with infusion fluids.

Each vial contains 230 mg of vosaroxin and is intended for single use. The proposed packaging material is a 25ml amber, type I, glass vial with a stopper, flip-off cap and overseal, and a carton as secondary packaging.

Drug product composition is relatively simple, comprising water for injections, sorbitol to achieve isotonicity, methanesulfonic acid to effect *in situ* salt formation and dissolution. The safety of D-sorbitol by an intravenous route and in the quantities proposed in the composition of Qinprezo has been justified.

Formulation development studies support the atypical choice of methanesulfonic acid as a counterion, based on solubility of the resulting salt and formulation robustness. While the pH of the resulting solution is very low (pH 2.0 – 3.0), this is accepted given that the drug product is given by slow central IV injection, where rapid dilution is expected. The formulation composition has remained consistent from non-clinical toxicology through pivotal clinical trials, primary stability and validation. The described minor changes in process are not clinically relevant as the drug product is a solution for injection with consistent composition. Compatibility with 'Infusion sets of polyvinylchloride (PVC) plastic containing diethylhexylphthalate (DEHP)', as described in section 6.6 of the SmPC, still needs to be demonstrated.

Manufacture is conventional, comprising formation of a vosaroxin suspension in aqueous sorbitol solution, in situ salt formation/dissolution, followed by aseptic filtration through two 0.22 µm filters in series, vial filling sealing and terminal (moist heat) sterilisation for NLT 20 minutes at 122^{o}C. Formal process validation studies are presented for three batches, manufactured at a proposed commercial

scale. All excipients are compendial (Ph. Eur.) quality with the exception of methanesulfonic acid, which is not the subject of a monograph in the Ph. Eur., BP or USP. Some outstanding questions remain with regard to the in-house specification for methanesulfonic acid.

The control strategy at release and over shelf-life is considered to be satisfactory.

The proposed primary pack comprises an amber type I glass vial and elastomer stopper with an aluminium overseal with a flip-off plastic cap. Stability data support a shelf-life of 24 months under no special temperature storage conditions, with cautions to keep the vial in the outer carton to protect from light and not to freeze.

3.1.4. Discussion on chemical, pharmaceutical and biological aspects

From a quality perspective, no major objections have been identified.

3.1.5. Conclusions on the chemical, pharmaceutical and biological aspects

From a quality perspective, a marketing authorisation could be granted upon satisfactory resolution of these concerns.

3.2. Non clinical aspects

3.2.1. Pharmacology

Vosaroxin is a DNA-intercalating topoisomerase II inhibitor. Vosaroxin's activity appears to be exclusively mediated through DNA intercalation and topoisomerase II inhibition. Vosaroxin, relative to other topoisomerase II inhibitors, is minimally metabolized and significant production of free radical formation, reactive oxygen species (ROS), toxic metabolites, DNA crosslinks, or DNA alkylation are not associated with its stable core quinolone structure. Vosaroxin causes replication-dependent, site-selective DNA double strand breaks (DSB) that lead to apoptosis in G/C-rich sequences that are characteristic of quinolone-induced DNA cleavage.

Vosaroxin induces G2/M arrest and S-phase lag. The S-phase lag may contribute to the synergy seen with vosaroxin in combination with cytarabine, as cytarabine is an S-phase active agent. Vosaroxin activity targets actively replicating cells, and the extent of DNA damage is cell cycle-dependent, with the damage induced in G2/M $\geq$ S >> G1. Rather than DNA DSB, the damage caused by vosaroxin in S-phase appears to be torsional stress due to cleavage complexes proximal to sites of DNA replication, causing the replication fork to stall and inducing DNA damage markers. In contrast, doxorubicin induces DNA fragmentation in S-phase and is associated with replication fork collapse. However, both agents cause DNA breaks in G2/M phase, and maximum cytotoxic activity occurs in this phase of the cell cycle.

As a downstream consequence of its inhibition of topoisomerase II-mediated DNA processing and DNA damage, vosaroxin inhibits DNA, RNA, and protein synthesis. Vosaroxin is a more potent inhibitor of protein synthesis than doxorubicin and etoposide. PD biomarkers consistent with vosaroxin mechanism of action were used to probe patient samples from a Phase 1b/2 study of vosaroxin in combination with cytarabine in relapsed or refractory AML, for evidence of a DNA damage response to vosaroxin treatment. Up-regulation of pDNA-PKcs and pCHK2 (both markers of DNA DSB) was detected within 2 hours post-dose in PBMC from 15 of 23 patients treated with $\geq$ 34 mg/m2 vosaroxin, providing clinical evidence of mechanism-based PD response.

Vosaroxin is stated not to be a substrate for the P-gp efflux transporter, but is a substrate for BCR. The activity of vosaroxin was evaluated in models of drug resistance with P-gp or BCRP overexpression that

also have reduced topoisomerase II levels; vosaroxin activity was reduced several fold, but was less affected than other topoisomerase II inhibitors. Vosaroxin was also active in biopsies deficient in p53 family members. These results, along with data from paired cell lines with and without functional p53 indicate that vosaroxin can induce apoptosis independent of p53. In support of this application, the applicant claims that vosaroxin evades two common mechanisms of drug resistance operative in resistance to epipodophyllotoxins, anthracyclines, and mitoxantrone.

The DNA double strand breaks caused by vosaroxin are repaired by HRR which is performed through the assembly and actions of a multiprotein complex that includes BRCA proteins. Cells deficient in BRCA2 function were 5-fold more sensitive to vosaroxin.

In vitro, vosaroxin had cytotoxic activity in a wide range of human cancer cell lines and in human primary tumour biopsies.

Ex-vivo, vosaroxin activity against AML, ovarian and breast cancer biopsies was compared with other cancer agents, including cisplatin, carboplatin, cytarabine, doxorubicin, and etoposide. Limited resistance to vosaroxin was observed. Similar ex vivo assessment in an adaption of the EDR assay of bone marrow aspirates from patients in both AML studies also indicated low resistance to vosaroxin. Both solid tumour and AML biopsies had more resistance to the chemotherapies tested than to vosaroxin.

In vivo vosaroxin was active against established human tumour xenograft mouse models and in syngeneic tumour mouse models, including two models of haematological malignancies. Vosaroxin was more active than etoposide and doxorubicin.

Vosaroxin in combination with cytarabine showed synergistic or additive activity in cell lines and synergy was demonstrated in primary patient AML samples. In normal mice receiving vosaroxin in combination with cytarabine, a reversible, greater than additive reduction in bone marrow cellularity and peripheral leukocytes was observed.

Secondary pharmacodynamic studies evaluated vosaroxin's potential for off-target activity in a panel of 80 transmembrane and soluble receptors, ion channels and monoamine transporters. Vosaroxin did not display significant inhibitory activity in this panel, with the exception of moderate inhibition (40%) of the muscarinic M2 receptor. Vosaroxin interaction with this acetylcholine receptor was further characterized and an IC50 of 6.2 µM (2.49 µg/mL) and Ki of 4.3 µM (1.72 µg/mL) were determined. Following administration of 90 mg/m2 vosaroxin to patients with haematological malignancies, average Cmax was 3.3 µg/mL (8.2 µM) total vosaroxin or 0.924 µg/mL (2.30 µM) unbound vosaroxin suggesting some inhibition of the muscarinic M2 receptor may occur. However, there is no clinical evidence of adverse effects related to inhibition of the muscarinic M2 receptor. Mucositis and other gastrointestinal adverse events including diarrhoea that are observed with vosaroxin may preclude detection of possible anticholinergic effects of the drug. Overall, the results of the study are consistent with the specificity of vosaroxin for topoisomerase II.

Vosaroxin belongs to the quinolone class of molecules. Therefore, the antimicrobial activity of vosaroxin was assessed against Enterococcus faecalis, Escherichia coli, Pseudomonas aeruginosa, and Staphylococcus aureus. Vosaroxin did not show antimicrobial activity in this assay, consistent with a compound specific for mammalian topoisomerase II. It is therefore unlikely that vosaroxin would exert antimicrobial activity, or inhibit quinolone antimicrobials used to treat infections.

Cumulative-dose cardiomyopathy is associated with the anthracylines and mitoxantrone. ROS and other toxic metabolites are implicated in this scaffold-based cardiomyopathy and therefore the propensity for vosaroxin to generate these species was investigated. A well-characterized mechanism of ROS formation is by Fe(III) complexation and redox cycling. Doxorubicin and vosaroxin bind Fe(III)

with comparable strength. However at physiological pH, doxorubicin forms a mixture of protonated ligand species while [Fe(vosaroxin)3] is the predominant species indicative of greater iron complex stability. The stable iron complexes formed by vosaroxin are claimed to be unlikely to produce the toxic metabolites and ROS associated with doxorubicin. These results are consistent with experiments in colorectal cancer cells showing that vosaroxin produced limited ROS in contrast to the levels produced by doxorubicin. These data provide evidence that vosaroxin may avoid cumulative cardiotoxicity.

Safety pharmacology studies revealed that there were no effects of single IV doses of vosaroxin up to 50 mg/kg (150 mg/m2) in mice on overall behaviour, locomotor activity, and reactivity to various stimuli (hot plate, electroshock, and acetic acid). With respect to the autonomic nervous system, acetylcholine-induced contractions were inhibited in isolated guinea pig ileal longitudinal muscle, consistent with inhibition of the muscarinic M2 receptor in biochemical assays.

In anesthetized dogs, there were no statistically significant effects on respiratory rate, heart rate or ECG parameters after IV administration of up to 10 mg/kg (200 mg/m2) vosaroxin. However, 1/4 dogs showed a transient increase in respiratory rate and a transient decrease in heart rate at the 10 mg/kg. The main effects on cardiovascular function following the IV administration at this dose were transient hypotension (~20–40% reduction in blood pressure that returned to baseline/control values within 10 minutes of administration) and a persistent reduction in femoral blood flow (34% reduction relative to baseline); no effects were noted at 1 or 3 mg/kg. No significant effects on ECG intervals were noted at doses up to 10 mg/kg in anesthetized dogs. The absence of effect on QTc is consistent with the absence of inhibition of hERG channels in vitro at concentrations up to 30 µM (12.03 µg/mL).

In conscious rats no effects on heart rate were observed after IV administration of up to 10 mg/kg (30 mg/m2) vosaroxin. On Day 4 at 10 mg/kg, systolic, mean, and diastolic blood pressures increased significantly (18%, 18% and 21%, respectively). Significant decreases in these parameters were seen on Day 8 (11 to 13%) at this dose level, suggesting a small but vosaroxin-related delayed effect on blood pressure.

Gastric emptying and/or gastric volume were reduced, and gastric pH was increased in rats at doses ≥ 3 mg/kg (18 mg/m2). Increases in spontaneous ileum contraction (rabbit) were seen with 100 μg/mL (249 μM) vosaroxin, but there was no effect on small intestinal charcoal meal transit in mouse. In vitro, 100 µg/mL (249 µM) vosaroxin had no effect on spontaneous contractions of isolated guinea pig atrium but there was a small 18% increase in contractile force. Vosaroxin had no clinically relevant effect on coagulation or platelet aggregation, as effects on PT and aPTT were only seen at concentrations ≥ 300 μg/mL (840 μM). Vosaroxin had no local anaesthetic effects when applied to the eyes of guinea pigs at concentrations up to100 μg/mL (249 μM).

In two separate studies conducted to assess effects on renal function in rats, no clearly consistent or dose-responsive effects on urine volume or electrolyte (sodium, chloride, and potassium) excretion were noted at doses up to 50 mg/kg (300 mg/m2).

3.2.2. Pharmacokinetics

The PK of vosaroxin was characterized after single IV bolus dose administration in mouse, rat, dog and monkey. In mice, rats, and monkeys, the plasma concentration of vosaroxin after a single IV bolus dose declined in a biphasic manner, resulting in terminal half-life (t½) of 4.1 to 5.5 hours. In dog, plasma concentration-time profiles were triphasic. Because of the apparent differences in disposition in dog versus rodent and monkey, no further studies were conducted in dog. The volume of distribution (Vd) was 7 L/kg in mice, 4.92 L/kg in rats and 0.73 – 0.80 L/kg in monkeys, exceeding total body water volume. In rodents and monkey, the AUCinf and the Cmax increased approximately dose proportionally. Overall, vosaroxin PK was independent of sex.

In rat, repeated dose PK was characterized in a 7-day repeat-dose PK study on Days 1 and 7. TK was evaluated on Days 1 and 88 in the 13-week intermittent-dose toxicity study in which vosaroxin was administered on Days 1, 4 every 28 days for 4 cycles. In both studies, exposure increased approximately dose proportionally. After daily administration of vosaroxin for 7 or 10 days, exposure (AUCinf) was similar for the first and last vosaroxin dose in both repeat-dose PK studies. However, in the 13-week intermittent dose study, exposure (AUCinf) increased up to 2.3-fold between Days 1 and 88; time-dependent PK was observed at all dose levels. These data suggest that in rat, the disposition of vosaroxin was affected following intermittent dosing over 13 weeks resulting in increased drug exposure.

In a repeated-dose study in monkey (males and females, qd x 14) TK exposure parameters were approximately dose proportional for the low and mid-dose groups but greater than dose proportional for the high dose group. TK parameters were similar on Days 1 and 14 suggesting vosaroxin disposition was unaffected by repeat-dosing for 14 days. In a 5-week intermittent dose toxicity study (q7d x 5) TK exposure parameters were approximately dose proportional and parameters on days 0 and day 28 were similar.

In a 13-week intermittent IV bolus study of vosaroxin in monkey (Days 1 and 4 q28d x 4) the dose was increased for the high-dose group for the final 2 cycles of treatment because of the absence of any clinical evidence of toxicity and the slight effects on haematology parameters after the first 2 cycles. The vosaroxin dose levels were 1.2, 6.0, and 18.0/30.0 mg/m2. Exposure parameters (Cmax and AUCinf) were approximately dose proportional across all dose levels on both Days 1 and 88, and no accumulation was observed for the low and mid-dose groups. Accumulation could not be evaluated for the high dose level because of the increase in dose in contrast to the analogous study in rat where increases in exposure over time were seen at all dose levels.

Only vosaroxin was measured in TK studies as plasma metabolites were qualitatively similar across species and present as minor metabolites only.

Protein binding of vosaroxin was evaluated in mouse, rat, monkey and human serum. Vosaroxin protein binding was lower in mouse (39%) and rat (55%) serum than in monkey (75%) and human (72%) serum.

In rat and monkey (the toxicology species) and human blood, vosaroxin did not preferentially partition into blood cells and concentrations in plasma were generally similar to (rat) or higher than (monkey, human) those in blood cells.

In KB nasopharyngeal tumour-bearing nude mice, after a single IV bolus dose of vosaroxin, tumour concentration was 5.5 to10.5 times higher than the plasma concentration, resulting in a tumour AUC0-inf that was 7.9 times higher than the corresponding plasma AUCinf.

In rats, radioactivity distributed rapidly and widely to the tissues after IV administration of 30 mg/m2 [14C] vosaroxin. Most tissues reached maximum concentrations within 30 minutes and showed tissue to plasma ratios > 2 with only brain tissues exhibiting tissue/plasma ratios of < 2. At 96 hours post-dose liver and bone were the only tissues with measurable radioactivity.

In vitro, vosaroxin undergoes minimal CYP450 and UGT mediated conjugative metabolism in rat, monkey and human microsomes, and there was no detectable metabolism in hepatocytes.

Metabolite profiling in vitro in rat, cynomolgus and human systems and in vivo in rat indicated that metabolic pathways for vosaroxin are glucuronide conjugation, oxidation, N dealkylation, and O dealkylation via several UGT isozymes and CYP1A2, CYP2D6 and CYP3A4. Metabolites were identified as dihydrovosaroxin, dihydrodecarboxylic acid vosaroxin, O desmethylvosaroxin, N desmethylvosaroxin, and an acyl glucoronide of vosaroxin.

Following IV administration of 60 mg/m2 [14C] vosaroxin to rats, vosaroxin was the major species present and accounted for 97%, 35% and 30% of the radioactivity found in plasma, urine and bile. N desmethylvosaroxin, the only plasma metabolite detected, accounted for < 3% of the total vosaroxin exposure.

In the monkey N-desmethylvosaroxin (M4) was the only metabolite detected in the systemic circulation and the Cmax of 22ng/mL, was reached at approximately 0.9 hours post-dose. Average N-desmethylvosaroxin exposure was 2.2% of the total exposure of unchanged vosaroxin.

Vosaroxin did not inhibit CYP450 isozymes 3A4, 2C9, 2D6, 1A2 and 2C19 in vitro (Ki > 100 µM; 40.1 µg/mL). Vosaroxin did not induce CYP450 isozymes 1A2, 2B6, 2C9, 2C19 and 3A4 in human hepatocytes. This suggests that the potential for clinically relevant interactions with vosaroxin and active substances that interact with these pathways is low.

Excretion of radioactivity in mouse and rat was rapid (77.7% and 83% complete in 24 hours). The majority of radioactivity (70.5% and 80.0%) was recovered in faeces whilst urine contained 7.2% and 15.7% of radioactivity respectively. In the monkey, urinary excretion accounted for 5% of the administered dose at 24 hours post-dose.

Biliary excretion was a major route of elimination. High concentrations of radioactivity found in the gallbladder of mice after IV administration of [14C] vosaroxin were attributed to excretion of radioactivity into bile. In bile duct cannulated rats, 37.9%, 32.5%, and 19.6% of radioactivity was recovered in bile, faeces and urine at 48 hours. After intra-duodenal administration of bile obtained from rats dosed with [14C] vosaroxin; an estimated 13.8% of an IV dose could be reabsorbed enterohepatically in rats.

3.2.3. Toxicology

The toxicity of vosaroxin following IV administration was characterized in single-dose toxicity studies in mouse, rat and cynomolgus monkey, and in 2-week repeated-dose and 5-week and 13-week intermittent-dose studies in rat and monkey. Also the following studies were conducted: a standard battery of in vitro and in vivo genotoxicity studies; fertility (male and female rats), reproductive and developmental toxicity studies in rat; local tolerance in rabbit; and other toxicity studies including evaluation of nephrotoxicity in rat, antigenicity in mouse, rabbit and guinea pig, and phototoxicity in vitro in 3T3 mouse fibroblasts. Toxicity studies were GLP-compliant and TK was conducted in those rat studies sponsored by Sunesis and in all cynomolgus monkey studies.

In single dose toxicity studies in mouse, rat, and monkey the MTD was exceeded. Animals died on study or were sacrificed in a moribund state. Deaths occurred at vosaroxin doses ≥107.4-144 mg/m2. The main target organs of toxicity common to all three species were the lympho-hematopoietic system, including the spleen and thymus (mouse and rat), the GI tract including the cecum, and the reproductive system including the testes. In addition in the monkey dose-dependent myelosuppression occurred across all dose level and the kidney was a target organ of toxicity in the male monkey.

The rat and cynomolgus monkey were selected as the species for the repeated dose toxicity studies based on ADME characteristics. Metabolite profiles in vitro were similar to that in humans and PK concentration-time profiles were biphasic and similar for both toxicology species.

In the repeated dose toxicity studies the main target organs were the lympho-haematopoietic system, the gastrointestinal (GI) tract and the reproductive system. In addition, there were other species specific adverse effects which occurred in the renal system (rat only), thickening of the stifle joint physis (rat only), alopecia (rat only) and at the injection site (monkey only). In the rat and monkey there was evidence of an adverse effect on the liver.

Lympho-haematopoietic system

Adverse effects of vosaroxin on the lympho-hematopoietic system occurred in all general toxicity studies. These effects were dose and dose regimen dependent, with increased severity at severely toxic doses (STD). Evidence of myelosuppression was seen in haematology parameters, including decreased WBC, RBC and platelets. There was lymphoid depletion in lymph nodes and bone marrow hypoplasia, hypocellularity, and necrosis. Extramedullary haematopoiesis, associated with STD in the single dose studies and with both the STD and non-STD (NSTD) level in the rat study of 5 weekly doses of vosaroxin was noted variously in spleen, thymus, liver, lymph nodes, cecum and adrenal gland.

Vosaroxin's effects on the lympho-hematopoietic system were reversible.

Gastrointestinal tract

Toxicity to the GI tract, in addition to occurring in the single dose studies in mouse, rat and monkey, also occurred in the 14-day repeated-dose study in rat. Diarrhea occurred in single dose studies at vosaroxin doses associated with moderate to severe toxicity and after daily vosaroxin doses of 10.8 mg/m2 (total dose administered). Pathological changes in the GI tract (doses ≥ 92.1 mg/m2) included dilation and discoloration of the tract; haemorrhage, erosion, degeneration, and necrosis of stomach and cecum; dark-red discoloration of the GI mucosa, distension of the cecum, haemorrhage or degeneration and necrosis of the mucosa of the GI tract, as well as inflammation or inflammatory cell infiltration (doses ≥ 72 mg/m2). GI toxicity was not seen in monkey other than in the single dose study, and was not observed in intermittent-dose studies in rat.

The data indicate that effects on this target tissue were species, dose and schedule dependent. Reversal of GI toxicity was seen in the rat repeated-dose study during the recovery phase, and regeneration of the mucosa was seen in surviving animals in the single dose toxicity studies indicating reversibility of these findings.

Reproductive system

Adverse effects on the male reproductive system were observed in mouse, rat and monkey in the single dose toxicity studies, and in rat repeated- and intermediate-dose toxicity studies. Atrophy of the testes, seminiferous tubules, seminal vesicles and epididymis occurred in single dose studies in rodents. In the monkey, single dose administration of 144 mg/m2 resulted in softened testes with dark red maculae and haemorrhage, and seminiferous tubule and epididymis epithelial cell vacuolation. However, there was no evidence of reproductive organ toxicity in repeated and intermittent-dose studies. In rat, seminal vessel atrophy was seen in the 14-day repeated-dose study at 10.8 mg/m2. After 5 weekly 30 mg/m2 doses of vosaroxin in rat, testis weight was significantly decreased and testes were softened and atrophic; the seminiferous tubule was also atrophied. Adverse findings in the 13-week intermittent study included decreased testis weight, degeneration of seminiferous tubules, debris in the cellular lumen of the epididymis, and hypospermia with severity and frequency increased at the higher vosaroxin doses. In female reproductive organs evidence of adverse effects were observed only in repeated dose studies in rat. Atrophy of the uterus, degeneration of ovarian follicles, and degeneration/regeneration of vaginal mucosa was seen at 10.8 mg/m2 in the 14-day toxicity study; degeneration of the ovary was seen in the high dose group after 5 weekly doses of 30 mg/m2 vosaroxin. In the 13-week study, decreased uterus weight was seen in the low and high dose levels.

Reproductive organ toxicity was not fully reversed during the 4-week recovery period. In view of the proposed therapeutic indication and the intended patient population, this finding should not be an impediment to the grant of a Marketing Authorisation.

Renal findings

Nephrotoxicity characterized by tubular epithelial degeneration and regeneration occurred in the 14-day repeated-dose study (≥ 4.32 mg/m2/day) and the 5-week (30 mg/m2/dose) and 13-week (18 mg/m2/dose administered Days 1 and 4, 36 mg/m2/cycle) intermittent-dose studies in rat, and in 1 monkey at a lethal dose of vosaroxin (288 mg/m2). In the 14-day repeated-dose rat study, these findings were present at ≥ 4.32 mg/m2/day after the 1-month recovery period but not at the completion of dosing. In the intermittent-dose study for 5 weeks rats at 30 mg/m2/dose showed nephrotoxicity at the completion of the dosing phase that progressed during a 5-week recovery period. In the 13-week toxicity study of vosaroxin administered on Days 1 and 4 every 28 days for 4 cycles increased urine volume and urine specific gravity was seen in male rats at doses ≥ 6.0 mg/m2 and moderate tubular degeneration was noted in the kidney at the terminal sacrifice in all males at 18 mg/m2/dose that was partially reversed after the 8-week recovery period. In a special study to further characterize vosaroxin-related nephrotoxicity and its reversibility more fully, histopathology revealed renal tubular degeneration and regeneration accompanied by karyomegaly and serum creatinine changes that appeared at 2 weeks post-dose, was consistently observed and more pronounced at 4 weeks post-dose, and showed partial reversibility at 8 weeks post-dose. In summary, vosaroxin caused dose- and schedule-related nephrotoxicity in rat characterized by degeneration of renal tubular epithelium that was partially reversed under the conditions studied. Similar histopathological changes were observed in one cynomolgus monkey that received a lethal vosaroxin dose. A guidance statement should be added to section 4.4 of the SPC that patients who experience a reduced absolute neutrophil count and platelet count, GI toxicity or an infection should routinely have their renal function tested. In addition, during the clinical studies, patients experienced many infections which may also be due to the fact that they have not been adequately treated with antibiotics or antifungal prophylaxis. These infections and its consequences may have masked potential nephrotoxicity. Therefore, (delayed) nephrotoxicity should also be added as an important potential risk in the RMP in the Safety specification (SII) in Module SVIII Summary of the safety concerns (OC).

Liver

In the rat, clinical chemistry parameters e.g. decreased triglycerides, bilirubin levels, increased cholesterol and phospholipid levels (males only), and microscopical observations e.g. focal necrosis and extramedullary haematopoiesis in the liver were noted in the 5 week study in which there were higher dose levels and shorter drug holidays compared to the 13 week study. In the 2 and 5 week studies in monkeys, brown pigment Kuppfer cells, periportal mononuclear cell infiltration and hypertrophy of the hepatocytes was observed. In humans, there has been an increase in liver specific markers albeit only in a small percentage (5%) of patients. The applicant clarified that in rats there was no clear association between serum chemistry changes and hepatic histopathological changes. The hepatic histopathological changes such as swelling of Kuppfer cells and extramedullary haematopoiesis were reversible. In monkeys there was no association between serum chemistry changes and hepatic histopathological changes. In addition, the hepatic histopathological changes such as brown pigment in Kuppfer cells, periportal mononuclear cell infiltration and hypertrophy of the hepatocytes were also seen in control animals. In humans, although there was an increase in liver specific markers this was not regarded a sign of hepatotoxicity.

Injection site findings

Injection site effects were seen in the single dose monkey study and included haemorrhage, fibrin deposits and formation of fibrous tissue and necrosis. There was no dose response relationship and reversibility could not be assessed. In the 13-week rat study injection site effects that reversed in recovery were seen in all dose levels and in vehicle control animals. These observations were minimal

to slight haemorrhage in some animals in all dose groups except the high dose group where moderate haemorrhage (2/15 rats) and inflammation was observed.

Other findings

In rat, thickening of the stifle joint physis was seen after completion of the dosing phase, but not following recovery, in the 14-day repeat-dose study at 4.32 mg/m2 and in the 5-week intermittent-dose study at the high dose level. This adverse effect was not observed in the single dose or 13-week intermittent-dose studies suggesting that this finding may be schedule-dependent. The joint physis thickening in rat may be related to the relatively young age of the animals (6 weeks at initiation of dosing) and increased susceptibility for such lesions in growing rats as opposed to mature rats.

Reversible alopecia was observed only in rat. In the single dose study alopecia occurred at doses ≥ 69.6 mg/m2, with the histopathologic correlate of hair follicle atrophy and regeneration seen at STD (≥ 136.2 mg/m2). Alopecia accompanied by hair follicle atrophy and regeneration was observed at NSTD and STD in the 14-day repeat-dose toxicity study and at the highest dose level in the 5-week intermittent-dose study. Thinning hair coat without microscopic findings was seen in the 13-week intermittent-dose study at the highest dose level.

Vosaroxin Cmax values were approximately 1.3- to 1.5-fold higher in rodent at lethal dose (LD)10 and 4.25-fold higher in monkey at the lowest LD relative to the Cmax values in patients treated with 90 mg/m2 vosaroxin; however, vosaroxin AUCinf values at these lethal dose levels in nonclinical species were exceeded in patients who received 90 mg/m2/dose vosaroxin (administered Days 1 and 4) in combination with 1 g/m2 cytarabine (administered Days 1 through 5).

In the rat repeated-dose toxicity studies NOAELs were identified at doses and exposures well below those achieved clinically. In the 13-week intermittent dose toxicity study in rat that mimicked the dose schedule in VOS-AML-301 for 4 cycles, the NOAEL was 1.2 mg/m2. At this dose level, on Day 1 and Day 88, AUCinf was 0.1258 µg•hr/mL and 0.2257 µg•hr/mL, and Cmax was 0.0314 µg/mL and 0.0466 µg/mL. Rodents appeared to be more sensitive to vosaroxin than the monkey, with signs of toxicity occurring at lower doses in rat and mouse. The applicant states that in the monkey studies, doses selected for the 14-day and 5-week repeated-dose studies performed by Dainippon were with hindsight overly conservative, perhaps in response to the toxicities observed in the single dose study at dose levels >36 mg/m2. In the 13-week intermittent dose toxicity study conducted by Sunesis, because of limited indications of toxicity, the dose was increased for the high dose group from 18 to 30 mg/m2 for the last 2 cycles.

Vosaroxin was positive in the Ames, chromosomal aberration, and in vivo mouse micronucleus assays. Consequently vosaroxin is genotoxic. These findings were anticipated given vosaroxin DNA damaging effects in replicating cell.

No carcinogenicity studies were conducted. This is acceptable in view of the intended patient population. In any case Vosaroxin is a likely carcinogen given its similar mechanism of action to known carcinogenic drugs and the positive results in genotoxicity assays. Furthermore, vosaroxin is to be administered with cytarabine which has been shown to be mutagenic and carcinogenic in animals.

In reproductive and developmental toxicity studies in rat, vosaroxin did not affect male or female fertility or the embryonic development of the F1 offspring of treated males at dose levels of 0.15 - 2.4 mg/m2 and 0.12 - 1.2 mg/m2 in females and males, respectively. In treated males at the high dose group (1.2 mg/m2), there were vosaroxin-related effects on hematological parameters consistent with myelosuppression and decreased thymus, spleen, testes and epididymis weights at necropsy with drug-related atrophy of the seminiferous tubules; the NOAEL for toxicity in the parental male rats was 0.12 mg/m2. Dams in the high dose group (2.4 mg/m2) had reduced body weight gain, food

consumption, and absolute thymus weights; decreases in ovary weights were considered to be secondary to high embryo-fetal mortality. Fetal examinations showed increased dead fetuses in dams at ≥ 0.6 mg/m2, and decreased live fetuses were observed in dams at 2.4 mg/m2. The NOEL of vosaroxin in dams was 0.6 mg/m2 and the NOEL for embryos and fetuses was 0.15 mg/m2. In view of the proposed therapeutic indication and the intended patient population this finding should not be an impediment to the grant of a Marketing Authorisation.

The effect of vosaroxin on embryo-fetal development was evaluated in rats administered IV vosaroxin (GD7-GD17; 0.6 - 4.8 mg/m2 in the dose range finding study and 0 – 1.8 mg/m2 in the definitive study). Treatment with vosaroxin was not associated with any effects upon pregnancy. However, the number of fetuses with gross (head, depressed eye bulge, body edema), soft tissue (brain ventricle dilation, microphthalmia) and numerous skeletal malformations were significantly increased in the vosaroxin high dose group (1.8 mg/m2/day; AUCinf 0.1983 µg•hr/mL and Cmax 0.0479 µg/mL). This study did not reproduce the finding of increased ventricular septal defects observed in the preliminary embryo-fetal development study; this defect has been seen in animals exposed to some drugs with quinolone structures (pazufloxacin and sparfloxacin). These findings indicate that vosaroxin has adverse effects on embryo/fetal development in the rat.

Based on ICH S9 one species is considered sufficient for evaluation of reproduction toxicology given the toxicities observed in rat. Pre- and post-natal studies are not required for anticancer agents, and studies in juvenile animals were not necessary because the proposed patient population is ≥ 60 years of age. It is not known if vosaroxin is excreted into milk or is subject to placental transfer.

The assessment of the local tolerance of vosaroxin formulated for clinical use in albino rabbit following single IV administration indicated that deposition of vosaroxin outside the vein may cause local irritation.

Vosaroxin was not antigenic in studies that assessed antibody formation and anaphylactic or delayed-type sensitivity reactions in mouse, rabbit, and guinea pig.

Specific studies to investigate immunotoxicological effects of vosaroxin were not conducted. The general toxicology studies conducted are considered sufficient to evaluate immunotoxicological potential as described in ICH guideline S9.

Specific studies to investigate vosaroxin metabolites have not been conducted. N-desmethylvosaroxin is the only circulating metabolite identified in rats, monkeys and human accounting for ≤ 3% of the total vosaroxin exposure. N-desmethylvosaroxin is adequately qualified in the nonclinical toxicology studies conducted and further studies are not warranted.

Specific studies to investigate impurities present in vosaroxin have not been conducted. Potential impurities and degradants present in vosaroxin drug substance and drug product were evaluated in nonclinical studies. All test article was of ≥ 98.7% purity and nonclinical batches were representative of clinical and commercial batches. The only specified impurity exceeding 0.15% is N-desmethylvosaroxin. The specification for this impurity, which is also present as a metabolite, is NMT 0.20%. Based on ICH Q3A (R2) and ICH S9, further studies of impurities that are also metabolites are not required.

Methanesulfonic acid is used as an acidifying agent to solubilize vosaroxin. The applicant states that precautions were taken to minimize levels of alkyl sulfonates that are implicated as genotoxic substances. Validated test methods were used to verify that potential genotoxic impurities were not above the TTC in either the excipient or resulting drug product. The specifications for methanesulfonic acid are stated to be tightly controlled and in-house specifications to address the alkyl methanesulfonate levels. The specifications of < 5 ppm each for EMS and MMS indicate that potential

levels in drug product are much lower than the nominal TTC outlined in ICH M7, i.e. < 1.5 µg/day (dose), based on the maximum possible daily dose of 200 mg vosaroxin as 20 mL vosaroxin IV, which contains 52 mg methanesulfonic acid.

Vosaroxin phototoxic potential was evaluated in vitro in the Neutral Red Uptake Phototoxicity Test. The effects of vosaroxin on Balb/c 3T3 mouse fibroblasts viability were determined with and without ultraviolet radiation (UVR) exposure. Vosaroxin demonstrated phototoxicity in this assay system. Photosensitivity reactions have been reported in two patients with AML during treatment with Qinprezo. This is reported in the SPC.

3.2.4. Ecotoxicity / environmental risk assessment

The vosaroxin PEC surfacewater value is below the action limit of 0.01 µg/L and is not a PBT substance as log Kow does not exceed 4.5.

Therefore vosaroxin is not expected to pose a risk to the environment.

3.2.5. Discussion on non-clinical aspects

Vosaroxin is stated to be a first-in-class, anticancer quinolone derivative. Vosaroxin intercalates DNA and inhibits topoisomerase II, inducing replication-dependent, site-selective, double-strand DNA breaks, S phase lag and G2/M arrest, leading to apoptosis. Vosaroxin activity appears to be exclusively mediated through DNA intercalation and topoisomerase II inhibition.

Vosaroxin, in combination with cytarabine, is indicated for the treatment of adult patients ≥ 60 years of age with relapsed or refractory acute myeloid leukemia (AML).

In vitro, vosaroxin had potent cytotoxic activity in 19 solid tumour and hematologic cancer cell lines and showed similar activity in 5 drug-resistant cell lines, including those that overexpress P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). The anti-proliferative activity of vosaroxin in combination with cytarabine was synergistic or additive in 3 leukemia cell lines

In vivo, anti-tumour effects of vosaroxin were studied in 19 human tumour xenograft and 3 syngeneic tumour mouse models. Vosaroxin demonstrated anti-tumour activity in 15 of 17 solid tumour cancer xenograft models from diverse tissue origins, with tumour growth inhibition (TGI) ranging from 63% to 88% compared with vehicle controls.

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.

Vosaroxin belongs to the quinolone class of molecules. Vosaroxin did not show antimicrobial activity consistent with a compound specific for mammalian topoisomerase II.

Vosaroxin is intended for IV administration. Following a single IV bolus administration to KB nasopharyngeal tumour-bearing nude mice, tumour concentration was 5.5 to10.5 times higher than the plasma concentration, resulting in a tumour AUC0nf that was 7.9 times higher than the corresponding plasma AUCinf. In rats, radioactivity distributed rapidly and widely to the tissues after IV administration of 30 mg/m2 [14C] vosaroxin. Most tissues reached maximum concentrations within 30 minutes and showed tissue to plasma ratios > 2 with only brain tissues exhibiting tissue/plasma ratios of < 2.

In vitro, vosaroxin undergoes minimal CYP450 and UGT mediated conjugative metabolism in rat, monkey and human microsomes, and there was no detectable metabolism in hepatocytes.

In vivo, following IV administration of 60 mg/m2 [14C] vosaroxin to rats, vosaroxin was the major species present and accounted for 97%, 35% and 30% of the radioactivity found in plasma, urine and bile. N desmethylvosaroxin, the only plasma metabolite detected, accounted for < 3% of the total vosaroxin exposure. In the monkey N-desmethylvosaroxin (M4) was the only metabolite detected in the systemic circulation and the Cmax of 22ng/mL, was reached at approximately 0.9 hours post-dose. Average N-desmethylvosaroxin exposure was 2.2% of the total exposure of unchanged vosaroxin.

Vosaroxin did not inhibit CYP450 isozymes 3A4, 2C9, 2D6, 1A2 and 2C19 in vitro (Ki > 100 µM; 40.1 µg/mL). Vosaroxin did not induce CYP450 isozymes 1A2, 2B6, 2C9, 2C19 and 3A4 in human hepatocytes. This suggests that the potential for clinically relevant interactions with vosaroxin and active substances that interact with these pathways is low.

Excretion of radioactivity in mouse and rat was rapid (77.7% and 83% complete in 24 hours). The majority of radioactivity (70.5% and 80.0%) was recovered in faeces whilst urine contained 7.2% and 15.7% of radioactivity. In the monkey, urinary excretion accounted for 5% of the administered dose at 24 hours post-dose.

The rat and cynomolgus monkey were selected as the species for the repeated dose toxicity studies based on ADME characteristics. In the repeated dose toxicity studies the main target organs were the lympho-haematopoietic system, the gastrointestinal (GI) tract and the reproductive system. In addition, there were other species specific adverse effects which occurred in the renal system (rat only), thickening of the stifle joint physis (rat only), alopecia (rat only) and at the injection site (monkey only).

Adverse effects of vosaroxin on the lympho-hematopoietic system were observed in all general toxicity studies. These effects were dose and dose regimen dependent, with increased severity at severely toxic doses. Vosaroxin's effects on the lympho-hematopoietic system were reversible.

Toxicity to the GI tract, occurred in the single dose studies in mouse, rat and monkey, and also in the 14-day repeated-dose study in rat. GI toxicity was not seen in monkey other than in the single dose study, and was not observed in intermittent-dose studies in rat, indicating that effects on this target tissue were species, dose and schedule dependent. Reversal of GI toxicity was seen in the rat repeated-dose study during the recovery phase, and regeneration of the mucosa was seen in surviving animals in the single dose toxicity studies indicating reversibility of these findings.

Adverse effects on the male reproductive system were observed in mouse, rat and monkey in the single dose toxicity studies, and in rat repeated- and intermediate-dose toxicity studies. In female reproductive organs evidence of adverse effects were observed only in repeated dose studies in rat. Reproductive organ toxicity was not fully reversed during the 4-week recovery period. In view of the proposed therapeutic indication and the intended patient population, this finding should not be an impediment to the grant of a Marketing Authorisation.

Nephrotoxicity characterized by tubular epithelial degeneration and regeneration occurred in the repeated-dose and intermittent dose studies in the rat but only in one monkey at a lethal dose. In a special study to further characterize vosaroxin-related nephrotoxicity and its reversibility more fully, histopathology revealed renal tubular degeneration and regeneration accompanied by karyomegaly and serum creatinine changes that appeared at 2 weeks post-dose, was consistently observed and more pronounced at 4 weeks post-dose, and showed partial reversibility at 8 weeks postdose. In summary, vosaroxin caused dose- and schedule-related nephrotoxicity in rat characterized by degeneration of renal tubular epithelium that was only partially reversed under the conditions studied. A guidance statement should be added to section 4.4 of the SPC that patients who experience a reduced absolute neutrophil count and platelet count, GI toxicity or an infection should routinely have their renal function tested. In addition, during the clinical studies, patients experienced many infections

which may also be due to the fact that they have not been adequately treated with antibiotics or antifungal prophylaxis. These infections and its consequences may have masked potential nephrotoxicity. Therefore, (delayed) nephrotoxicity should also be added as a important potential risk in the RMP in the Safety specification (SII) in Module SVIII Summary of the safety concerns.

Vosaroxin is genotoxic. No carcinogenicity studies were conducted. This is acceptable in view of the intended patient population. In any case vosaroxin is likely to be a carcinogen given its similar mechanism of action to known carcinogenic drugs and the positive results in genotoxicity assays. Furthermore, vosaroxin is to be administered with cytarabine which has been shown to be mutagenic and carcinogenic in animals.

In reproductive and developmental toxicity studies in rat, fetal examinations showed increased dead fetuses in dams at ≥ 0.6 mg/m2, and decreased live fetuses in dams at 2.4 mg/m2. The NOEL of vosaroxin in dams was 0.6 mg/m2 and the NOEL for embryos and fetuses was 0.15 mg/m2. In view of the proposed therapeutic indication and the intended patient population this finding should not be an impediment to the grant of a Marketing Authorisation.

The effect of vosaroxin on embryo-fetal development was evaluated in rats administered IV vosaroxin (GD7-GD17). The number of fetuses with gross (head, depressed eye bulge, body edema), soft tissue (brain ventricle dilation, microphthalmia) and numerous skeletal malformations were significantly increased in the vosaroxin high dose group (1.8 mg/m2/day) .These findings indicate that vosaroxin has adverse effects on embryo/fetal development in the rat.

Based on ICH S9 one species is considered sufficient for evaluation of reproduction toxicology given the toxicities observed in rat. Pre- and post-natal studies are not required for anticancer agents, and studies in juvenile animals were not necessary because the proposed patient population is ≥ 60 years of age.

In vitro, in the Neutral Red Uptake phototoxicity test, vosaroxin was shown to have phototoxic potential.

3.2.6. Conclusion on non-clinical aspects

There are several adverse findings in the non-clinical toxicity package. These included effects on the on the lympho-hematopoietic system and on the GI tract, however these were reversible.

There were adverse effects on the male and female reproductive systems, which were not fully reversible in the recovery period. There were also severe adverse effects on developmental toxicity in the rat. In view of the proposed therapeutic indication and the intended patient population (≥ 60 years of age) this finding should not be an impediment to the grant of a Marketing Authorisation. Furthermore, vosaroxin is to be administered with cytarabine which has been shown to be mutagenic and carcinogenic and toxic to reproduction in animals.

Vosaroxin caused dose- and schedule-related nephrotoxicity in rat characterized by degeneration of renal tubular epithelium that was only partially reversed under the conditions studied. There are also clinical issues as a consequence of which a guidance statement (see above) should be added to section 4.4 of the SPC and furthermore delayed nephrotoxicity should be added as an important risk in the RMP in the Safety specification (SII) in module SVIII Summary of the safety concerns.

In summary, there are no major objections. One outstanding issue is that section 4.4 of the SPC should have a guidance statement added and the SII of the RMP should be amended as indicated above. From the non-clinical point of view, a marketing authorisation could be granted upon satisfactory resolution of this issue.

3.3. Clinical aspects

The sponsor has conducted 11 clinical studies of vosaroxin out of which four were in hematologic malignancies (as in table below). Additionally, vosaroxin has been investigated as a single agent in 7 advanced solid tumour studies, including small cell lung cancer, non-small cell lung cancer, and platinum-resistant ovarian cancer.

Tabular overview of clinical studies

Study	Study Population[a]	Study Design	Treatment (IV)	Endpoints
VOS-AML-301 (VALOR) Efficacy and Safety	AML (first relapsed or refractory) 711/705	Phase 3, randomized, controlled, double-blind, parallel group, multinational, adaptive design 101 sites US, Canada, Europe, New Zealand, Korea	<u>Group A:</u> Vosaroxin + cytarabine Vosaroxin Days 1, 4 90 mg/m^2 induction; 70 mg/m^2 (other cycles) Cytarabine Days 1-5 (2 h infusion) 1 g/m^2 daily <u>Group B:</u> Placebo + cytarabine Placebo (match vosaroxin) Cytarabine Days 1-5 (2 h infusion) 1 g/m^2 daily Up to 4 cycles	Primary OS Secondary CR Tertiary ORR, EFS, LFS, Remission rates, Subsequent transplant/AML therapy ECG/PK sub study (DRN101-367)
SPO-0012 Efficacy and Safety and Tolerability	AML (relapsed or refractory with 1−3 prior regimens 110/108	Phase 1b/2, open-label, multicenter, dose-escalation, expansion at MTD 7 US sites	<u>Sch A:</u> vosaroxin Days 1, 4 10 mg/m^2 escalation up to 90 mg/m^2 cytarabine 24-hour CIV 400 mg/m^2/day × 5 days <u>Sch B:</u> vosaroxin Days 1, 4 70 mg/m^2 escalation up to 90 mg/m^2 cytarabine 2-hr IV 1 g/m^2/day × 5 days Up to 4 cycles	Primary Safety/tolerability Secondary CR+CRp LFS OS
SPO-0014 Efficacy and Safety	Untreated AML (de novo or secondary) 113/113	Phase 2, open-label, multicenter 17 US sites	<u>Sch A</u>: vosaroxin 72 mg/m^2 once weekly x 3 wks (Days 1, 8, 15) <u>Sch B:</u> vosaroxin 72 mg/m^2 once weekly x 2 wks (Days 1, 8) <u>Sch C</u>: vosaroxin 72, 90 mg/m^2 twice weekly x 1 wk (Days 1, 4) Up to 4 cycles	Primary CR+CRp Secondary LFS OS

Study	Study Population[a]	Study Design	Treatment (IV)	Endpoints
SPO-0004 Safety, Tolerability, and PK	Advanced hematology malignancies 75/73	Phase 1b, open-label, multicenter, dose-escalation 4 US sites	Sch A: vosaroxin once weekly x 3 weeks (Days 1, 8, 15) 18 mg/m^2 escalation up to 90 mg/m^2 Sch B: vosaroxin twice-weekly x 2 weeks (Days 1, 4, 8, 11) for 4 doses 9 mg/m^2 escalation up to 50 mg/m^2 Up to 4 cycles	safety /tolerability PK recommend dose regimen for future Phase 2 studies
VOS-ADME-101 PK	Advanced solid tumors 6	Phase 1, open-label	[14C]-vosaroxin - IV on Day 1 Cycle 1 (28-day cycle) Vosaroxin IV on Day 1 of Cycles 2-4 (28-day cycles)	PK

[a] number of patients enrolled/treated; CIV: continuous intravenous infusion

3.3.1. Pharmacokinetics

Protein binding in human serum was approximated to be 72 and 73% at vosaroxin concentrations of 1 and 10 µg/mL, respectively. In vitro data indicate that vosaroxin is equally distributed between plasma and whole blood at both concentration of 1 and 50 µM. The reported volume of distribution is 120 L, indicating (extensive) distribution to the tissues. As calculated from the non-compartmental analyses of the various PK studies and the popPK model, clearance was approximately 4 L/hr with a terminal half-life (t½) of approximately 25 hours.

In the VOS-ADME-101 study, recovery of radioactivity was somewhat low with approximately 81% of total dose administered being recovered. The radioactivity found in feces (53%) and urine (28%) was collected up to 528 hr and 216 hr post dose, respectively. Clinical studies suggest that N-desmethylvosaroxin is the only metabolite identified in plasma and accounted for < 3% of the total vosaroxin exposure and that approximately 30% of the AUC is unaccounted for.

From both the non-compartmental PK analyses of the individual studies and the popPK model it can be concluded that the PK of vosaroxin is dose proportional for both the Cmax and the AUC over the dose range 9 to 90 mg/m^2.

The inter- and intra-individual variability in the PK of Cmax of vosaroxin was moderate to high, while for AUC inter-individual variability was moderate.

The popPK final model developed described the PK of vosaroxin with a 3-compartment model with first order elimination in the study population. Body weight was a covariate on the respective compartment volumes however body weight, BSA, and BMI were not found to be covariates on clearance. Age, race, and ethnicity or co-administered cytarabine were not significant covariates on the PK of vosaroxin.

Around 42.7% of the IV dose of vosaroxin is excreted via faeces and 27.7% via urine However, 30% of the radioactivity was not recovered within a period of 0-168 h and the percentage excreted unchanged in faeces and urine is 40%.

It appears that vosaroxin does not lead to inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1at the concentrations studied, , in vitro inhibition was observed at 100 µM for CYP2D6 and 3A4. The in vitro inhibition potential of vosaroxin for CYP3A4 at clinically relevant concentrations and potential DDI due to OATP1B1 inhibition should be discussed or modelled using PBPK modelling.

Vosaroxin may be a clinically relevant inhibitor of UGT1A8, but not of UGT1A1, 1A3, 1A4, 2B7 and 2B15.

Vosaroxin is not a substrate for P-gp yet is a substrate the BCRP transporter. Vosaroxin dose-dependently inhibited the BCRP-, MDR1- and MRP2 transporter-mediated probe substrate accumulation. Vosaroxin inhibited the OATP1B1- , OATP1B3- , OAT3- , MATE1- and MATE2-K transporter-mediated probe substrate accumulation. Vosaroxin was shown to be an unlikely substrate for the BSEP-, MRP2-, OATP1B1-, OATP1B3-, OCT1- and MATE1-transporters. Vosaroxin is a substrate of MATE2-K transporter (>2-fold accumulation) but it is unlikely to be a substrate for OAT1, OAT3 or OCT2.

There appears to be minimal interaction of the cytarabine on vosaroxin.

3.3.2. Pharmacodynamics

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

Vosaroxin antineoplastic activity appears to be exclusively mediated through DNA intercalation and topoisomerase II inhibition. In comparison to approved topoisomerase II inhibitors, vosaroxin is minimally metabolized and significant production of free radicals, reactive oxygen species (ROS), toxic metabolites, DNA crosslinks, or DNA alkylation are not associated with its stable core quinolone structure. This is in contrast to the epipodophyllotoxins (etoposide and teniposide), anthracyclines (doxorubicin and others) and anthracenediones (mitoxantrone) which exhibit non-topoisomerase II-dependent DNA damage activity as a result of metabolic activation and oxidative stress. This activity leads to free radical and ROS formation which causes point mutations, DNA adducts and cross links ROS implicated in the cumulative dose-dependent risk of congestive heart failure seen with anthracycline and anthracenedione scaffolds. Vosaroxin can be an alternative therapy to AML patients who have exceeded safe thresholds for anthracyclines or who are at high risk for treatment-related cardiac toxicity.

Vosaroxin is not a P-glycoprotein (also referred to as multi-drug resistance protein 1) substrate and its activity is independent of the p53 family of proteins; thus, it evades 2 common drug resistance pathways.

Vosaroxin demonstrated broad cytotoxic activity against cancer cell lines, patient biopsies, and in mouse models and had additive or synergistic activity in combination with a number of anticancer agents. In combination with cytarabine, vosaroxin showed synergistic activity in AML patient samples.

Vosaroxin has been investigated as a single agent in adult patients with hematologic malignancies and with solid tumours (small cell lung cancer, non-small cell lung cancer, and platinum resistant ovarian cancer). It has also been investigated in combination with different cytarabine regimens in adult patients with advanced AML. Promising activity was detected in early phase clinical studies in AML.

DNA damage consistent with vosaroxin mechanism of action was detected in analyses of peripheral blood mononuclear cells (PBMC) isolated from patients treated with vosoaroxin and cytarabine in combination (Study SPO-0012).

A subset of 21 patients from the pivotal study (VALOR) who participated in the ECG and PK substudy (DRN101-0367) showed no QTc effects related to vosaroxin, cytarabine, and the metabolites N-desmethylvosaroxin and 1-β-D-arabinofuranosyluracil (Ara-U). These results are in line with non-clinical data.

Vosaroxin and cytarabine AUC are higher in patients with higher BSA (median 1.92 m^2, range 1.92 to 2.60 m^2) compared to lower BSA (median 1.70 m^2, range 1.20 to <1.92 m^2). The clinical PK-PD relationship suggests that the dose administered is at or near E_{max}. Thus, BSA-based dosing of vosaroxin do not compromise the efficacy in patients with low BSA. The PK is not different in patients <60 years of age and >60 years of age.

There was no apparent relationship between vosaroxin exposure and grade of neutropenia, SOC infection grade, pneumonia grade, grade of mucositis, and fatal Severe Adverse Events. Thus, safety does not appear to be affected by vosaroxin exposure, and therefore dose adjusting by BSA does not appear to negatively impact safety.

3.3.3. Discussion on clinical pharmacology

Overall the clinical pharmacology data are sufficient for assessment.

Vosaroxin is a topoisomerase II inhibitor with an advantage over other drugs with similar mechanism due to the apparent lack of cardiac toxicity. Although anthracyclines and other extensively used topoisomerase II inhibitors are considered to be among the most active drugs in AML treatment their use have been limited by the cumulative dose related cardiac toxicity. This advantage is considered a clinically significant benefit in the AML relapse/refractory setting where patients not only need further treatment to control the disease but also need alternative options with an improved safety profile.

3.3.4. Conclusions on clinical pharmacology

There are no objections to an approval from a clinical pharmacology point of view, provided that the applicant submits acceptable responses to the other concerns raised.

3.3.5. Clinical efficacy

Dose-response studies and main clinical studies

Dose-response studies and main clinical studies

Efficacy is provided from a single pivotal study (VALOR study) supported by studies SPO-0012 and SPO-0014.

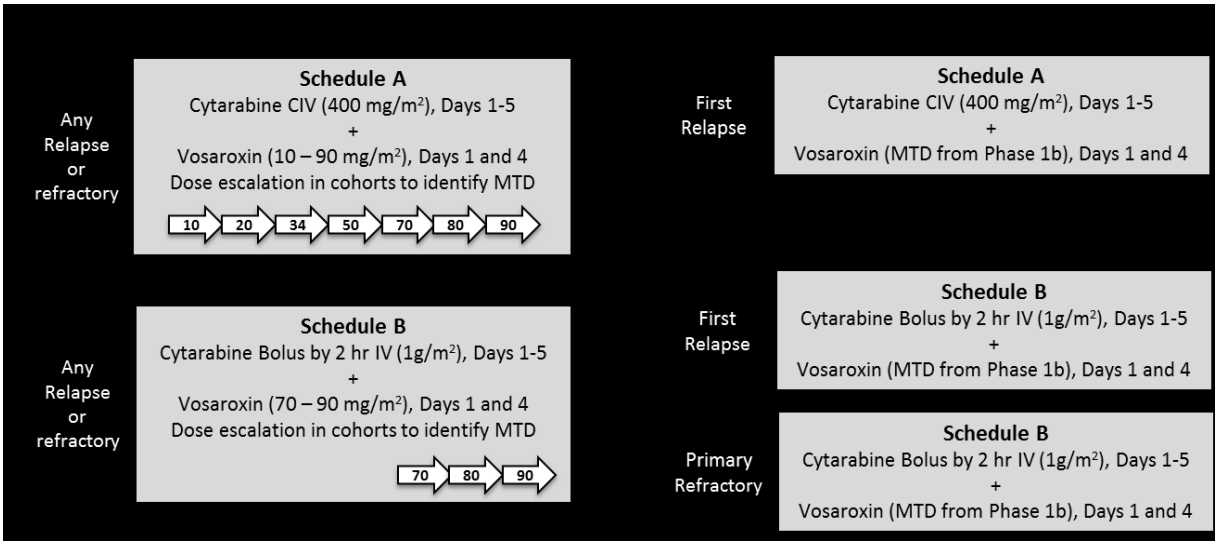
Dose response study - Study SPO-0012

This was a Phase 1b/2, open-label study using a dose-escalation design with expansion at the maximum tolerated dose (MTD).

The primary objective was to assess the safety/tolerability of vosaroxin in combination with cytarabine in patients with relapsed or refractory AML. Efficacy was assessed by combined remission rates (CR + CRp, modified IWG criteria), LFS, and OS (follow up for 2 years).

Eligible patients (≥18 years) had relapsed or refractory AML (de novo or secondary). In the dose-escalation phase, patients could have received 1 to 3 prior AML regimens. In the expansion phase, only patients with AML in first relapse (Schedules A and B) and those with primary refractory disease (Schedule B only) were eligible. Patients with prior allogeneic transplant, acute promyelocytic leukaemia or CNS involvement were excluded from study.

Two dosing schedules were employed as summarised below and patients received up to 4 cycles of treatment (1-2 cycles of induction and 1-2 cycles of consolidation).



MTD, maximum tolerated dose; CIV, continuous intravenous

Analysis was conducted for two populations, all enrolled patients who received any investigational medicinal product (All Treated Population, n = 108) and all first relapsed and primary refractory patients in the dose-escalation or expansion phase of either schedule who received 80 or 90 mg/m^2 of vosaroxin (Pooled Population, n = 71)

The first patient was enrolled on 6th October 2007 and last visit for the last patient treated was on 15th February 2012 in US. The majority were white (82.4%) and male (66.7%) with mean age 56.3 years (range 18 to 74), had primary refractory disease (57.4%) and had completed only 1 cycle of study treatment (79.6%)

The MTD of vosaroxin was established at 80 mg/m^2 for Schedule A and 90 mg/m^{2}for Schedule B. These doses were used in the expansion phase.

In the All Treated analysis (n=108):

- Total of 27 patients (25%) achieved CR or CRp (24 CR / 3 CRp) across both cytarabine schedules (24-hour CIV infusion or 2-hour IV infusion) and in patients with primary refractory and first relapsed disease. The percentage of patients achieving remission was similar among the treatment groups with the exception of those with sch A/first relapse/80 mg/m^2, which had a higher remission rate.
- Median LFS 11.6 months (range, 0.5 to 32.7). The longest reported median LFS was 25.2 months in schedule B first relapse.
- Median OS was 6.2 months (range, 0.2 to 33.7 ; 95% CI: 4.1, 7.7). The longest median survival was 8 months for Sch B, 70 to 90 mg/m^2. All Schedule B groups had longer median OS rates than Schedule A.

In the pooled analysis population (n = 71)

- CR/CRp 26.8% (19 patients), similar in patients with first relapse (11/37 patients, 29.7%) and with primary refractory (8/34 patients, 23.5%)
- Median LFS 25.2 months (range, 0.5 to 32.7)
- Median OS 6.9 months (95% CI: 4.4, 10.1). The OS for the primary refractory and the first relapse patients were similar (median OS 6.7 months and 7.1 months, respectively).

Both dosing schedules were found of acceptable tolerability but stomatitis was less frequent with short-infusion compared with continuous IV administration of cytarabine. Serious AEs were of higher incidence in schedule A than B (51.8% vs 40.4%).

In conclusion, vosaroxin in combination with cytarabine demonstrated clinically significant anti-leukemic activity in patients with relapsed or refractory AML. Cytarabine administered over 2 hours showed a more tolerable profile than when given as 24 hours continuous infusion and reported the longest median OS. The MTD of vosaroxin given on days 1 and 4 of each cycle was established at 90 mg/m^2 for schedule B. This study provided the rationale for selection of the dose and schedule used in the pivotal Phase 3 trial (VALOR).

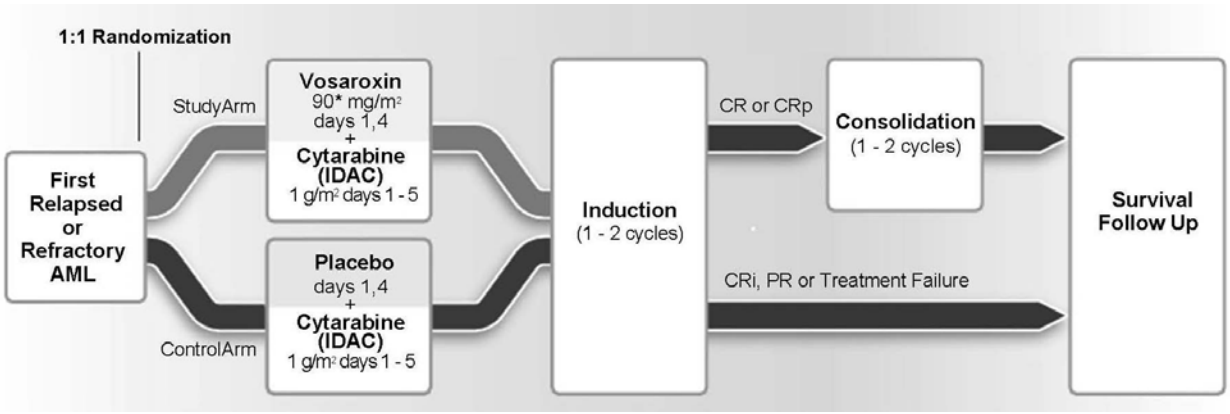
Post-hoc analyses in the subgroup of patients ≥ 60 years showed a CR rate of 23.2% and median OS of 7.1 months based on the All Treated analysis Set (n=56) and a CR rate of 23.7% and median OS of 6.8 months based on the Pooled analysis set (n=38).

Main study VOS-AML-301 (VALOR study)

Date of Report: 6 November 2015

This was a Phase 3, randomized, controlled, parallel group, double-blind, multinational clinical study of the efficacy and safety of vosaroxin and cytarabine versus placebo and cytarabine in patients with first relapsed or refractory AML.

Figure 1 Overall Study Design



*Vosaroxin 90 mg/m^2 on Days 1, 4; 70 mg/m^2 for all other cycles.

AML, acute myeloid leukemia; CR, complete remission; CRi, CR with incomplete recover of platelets or neutrophils; CRp, CR with incomplete platelet recovery; IDAC, intermediate-dose ara-C; PR, partial remission.

The study included four periods:

- Screening
- Treatment / hematologic recovery period with up to 2 cycles of induction and up to 2 cycles of consolidation. An assessment on Day 15 of Induction 1 and 2 was performed to evaluate leukemic activity by local laboratories and could be repeated at Investigator discretion. Complete blood counts (CBC) were examined at least weekly thereafter to monitor for hematologic recovery. Within 14 days of hematologic recovery or by Day 57, whichever occurred first, a bone marrow biopsy or aspirate and CBC was obtained to document disease response based on modified IWG response criteria.

  Induction 2 was recommended if the Induction 1 assessment indicated residual leukaemia (≥ 5% blasts), and if a second cycle was indicated in the judgment of the Investigator or if the Induction 1 response assessment was PR. Induction 2 must have begun by Day 57 of Induction 1. Response was determined as for Induction 1. Treatment was discontinued after Induction 2 if no CR, CRp, or CRi was achieved.

  If a CR or CRp was achieved by Day 57 after Induction 1 or Induction 2 (8 weeks after the first dose in the cycle), up to 2 cycles of consolidation could have been completed if safety parameters were met.

  If a CRi was achieved by Day 57 of Induction 1 or Induction 2, consolidation could have been considered if hematologic recovery occurred by Day 85 (12 weeks after the first dose in the cycle).

  Consolidation was optional but confirmed CR or CRp, resolution of prior treatment related toxicity, adequate renal and liver function, and ECOG performance status ≤2 were required. Bone marrow monitoring during consolidation and follow up was per standard of care. Consolidation 1 must have begun no later than Day 85 (12 weeks after Day 1 of the previous induction cycle).

  Treatment was discontinued after a maximum of 4 cycles or assessment indicated resistant disease or relapse, whichever occurred first.

  Patients who had a bone marrow or stem cell donor and were considered by their local site to be candidates for transplantation were expected to receive allogeneic transplantation after 1 or more cycles of study treatment. The transplantation type (allogeneic or autologous) and protocol were determined by each transplant centre.

- Post-treatment follow up (monthly during 1st year, every 2 months during 2nd year, and every 3 months thereafter) was conducted for all patients after treatment was either completed or discontinued for any reason. Information about disease status, survival, and subsequent non-protocol treatment for AML was obtained for all patients, including those who had transplantation.
- Long-term survival follow-up (every 4 months) began for all ongoing patients upon notification that the required number of deaths had occurred.

- **Study participants**

Inclusion criteria

- Age ≥ 18 years with AML (WHO classification)
- First relapsed or refractory AML with at least 5% blasts by bone marrow biopsy or aspirate, or at least 1% blasts in peripheral blood and met the following criteria:

FIRST RELAPSED

Must have met (a), (b), and (c)

(a) Had a first relapse occur at least 90 days to 24 months after the first CR or CRp

(b) Had a first CR or CRp after no more than 2 cycles of chemotherapy. At least 1 induction cycle must have consisted of an anthracycline (or anthracenedione) and cytarabine combination with a reasonable schedule/dose of anthracycline.

(c) Re-emergence ≥ 5% leukemic blasts in bone marrow not attributable to other causes or re-emergence ≥ 1% blasts in peripheral blood not attributable to other causes

Allowed

- Unlimited cycles/regimens of consolidation for first CR or CRp
- Transplantation for AML (allogeneic or autologous) unless within 90 days of randomization
- Maintenance therapy with hypomethylating or biologic agents until first relapse

REFRACTORY

Must have met (d) and (f) OR (e) and (f)

(d) Persistent AML at least 28 days after Day 1 of the first induction cycle of 1 or 2 cycles of cytotoxic chemotherapy

(e) Re-emergence ≥5% leukemic blasts in bone marrow or at least 1% blasts in peripheral blood not attributable to other causes, and was less than 90 days after the first CR or CRp

(f) Prior induction therapy that must have included no more than 2 cycles of cytotoxic chemotherapy. At least 1 induction cycle must have consisted of an anthracycline (or anthracenedione) and cytarabine combination with a reasonable schedule/dose of anthracycline in the judgment of the Investigator

- ECOG performance status of 0, 1, or 2
- Serum creatinine ≤ 2.0 mg/dL, total bilirubin ≤ 1.5 × ULN(unless due to Gilbert syndrome), AST ≤ 2.5 × ULN, ALT ≤ 2.5 × ULN
- Left ventricular ejection fraction at least 40%
- Clinically significant non-hematologic toxicity after prior chemotherapy recovered to Grade 1
- Females must have been sterile or postmenopausal or if of childbearing potential, must have had a negative pregnancy test within 14 days before randomization, and must have agreed to use an adequate method of contraception during the study and until 30 days after the last treatment. Males must have been surgically or biological sterile, or agreed to use an adequate method of contraception during the study until 30 days after the last treatment.

Exclusion criteria

- Acute promyelocytic leukaemia
- More than 2 cycles of AML induction therapy
- Completed a single cycle of treatment containing a total dose of ≥ 5 g/m^2 cytarabine within 90 days before randomization
- Allogeneic bone marrow transplant for AML with infusion of stem cells within 90 days before randomization, or was on an active immunosuppressive therapy (GVHD) or had GVHD prophylaxis within 2 weeks before randomization
- Known or suspected central nervous system involvement
- Had other active malignancies (including other hematologic malignancies) or other malignancies within 12 months before randomization, except non-melanoma skin cancer or cervical intraepithelial neoplasia
- Uncontrolled active infection of any type. Infections under control with antibiotic treatment and chronic hepatitis were acceptable.
- Uncontrolled invasive fungal infection
- Prior myocardial infarction, unstable angina, cerebrovascular accident, or transient ischemic attack within 3 months before randomization
- Prior or current therapy with hydroxyurea or medications to reduce blast count within 24 hour before randomization
- Was required to have haemodialysis or peritoneal dialysis
- Pregnant or breastfeeding
- HIV seropositivity

- **Treatments**

Group A (vosaroxin/cytarabine)

Vosaroxin	Days 1 and 4: 90 mg/m^2 Induction 1; 70 mg/m^2 all other cycles
	Short intravenous (IV) infusion within 10 minutes
Cytarabine	1 g/m^2 daily on Days 1 through 5 (IDAC) as a 2 hour infusion

Group B (placebo/cytarabine)

Placebo	Days 1 and 4: volume matched to vosaroxin
	Short intravenous (IV) infusion within 10 minutes
Cytarabine	1 g/m^2 daily on Days 1 through 5 ("Intermediate" dose) as a 2 hour infusion

Dosing was capped at a maximum BSA of 2.4 m^2.

Each cycle was a minimum of 14 days and a maximum of 12 weeks. Treatment was administered for a maximum of 4 cycles or when assessment indicated resistant disease or relapse, whichever occurred first.

The use of medications for prophylaxis of nausea, vomiting, and infections was recommended and medications for managing myelosuppression (myeloid growth factors) or for prevention of tumour lysis syndrome were allowed at the discretion of the investigator.

- **Endpoints**

Primary	Overall survival (OS)
Secondary	Complete remission (CR)
Tertiary	CR + CRp (CR incomplete platelet recovery) rate
	Combined CR rate: CR + CRp + CRi (CR incomplete blood count recovery)
	Overall remission rate (CR + CRp + CRi + PR)
	Event- free survival: time from randomization until relapse for responding patients and time until treatment failure for non-responders
	Leukaemia- free survival: duration of response in patients with CR, from the start of CR until death or relapse, whichever is earlier for CR, for CR + CRp, and for combined CR
	Percentage of patients who have subsequent transplantation
	Percentage of patients who receive subsequent non-protocol AML therapy (including transplantation)

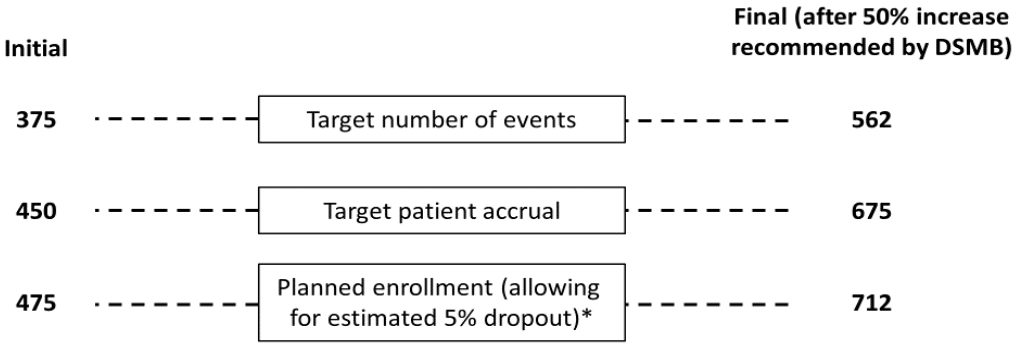
A blinded, independent, **C**entral **P**athology and **R**esponse **R**eview (CPARR) panel adjudicated the best clinical response for secondary and tertiary endpoints using modified IWG criteria and confirmed the entry criteria of diagnosis of relapsed or refractory disease AML at baseline. The CPARR review was independent of Investigator assessment. The level of concordance of the CPARR and Investigator assessments for CR and AML diagnosis at baseline was determined.

- **Sample size**

The sample size was based on comparison of OS between treatment arms at a 2 sided significance level of 0.05, assuming median survival was 5 months in the placebo arm with a 40% increase to 7 months in the vosaroxin arm. To meet a power requirement of 90%, the target number of events (deaths) is pre-specified to be 375. Four hundred fifty patients will be required to reach 375 events, assuming uniform accrual over 24 months and 6 months of follow-up after the last randomisation. Allowing for a 5% dropout rate the initial target accrual will be increased to 475 patients.

An effective sample size of 450 patients will provide 85% power to detect a difference between treatment groups in the secondary efficacy endpoint, CR rate, at a 2-sided significance level of 0.05, assuming CR rate is 10% in the placebo group and 20% in the vosaroxin.

The study was of adaptive design that allowed for the potential of a single 50% increase in the target number of events based on the interim analysis results:.



*The anticipated drop out rate was revised in the protocol from 10% to 5% as of 15 August 2012.

- **Randomisation**

A permuted block randomization (1:1) was used for treatment assignment stratified by 3 factors:

- disease status (refractory, *early* first relapse with duration of first CR or CRp ≥ 90 days and < 12 months, or *late* first relapse with duration of first CR or CRp ≥ 12 months and ≤ 24 months),
- age (< 60 years or ≥ 60 years)
- Geographic location (US or outside US).

- **Blinding**

Vosaroxin or placebo was administered in a double-blinded manner and cytarabine was administered in an un-blinded manner.

All patients, study site personnel, and the sponsor were blinded to treatment assignment.

- **Statistical methods**

The assumed hazard ratio to design the VALOR study was based on the results of the uncontrolled Phase 2 study (SPO-0012). There was uncertainty around the true incremental treatment effect with vosaroxin/cytarabine versus control. An adaptive design was employed to prevent the power from deteriorating if there were a smaller difference between the planned and true magnitude of the treatment effect.

An independent DSMB could recommend one of four actions based on results from an interim analysis planned after 187 deaths had occurred or 20 months after randomisation of the first patient, whichever occurs first: terminate the study for efficacy, terminate the study for futility, increase the target number of events by 50% or continue the study as planned.

The interim analysis was performed by an independent statistics provider. The efficacy boundary (one-sided significance level of 0.001525 for interim and 0.0247 for the final analysis) was based on the O'Brien-Fleming efficacy boundary derived from the Lan and DeMets error spending function.

Analysis populations:

Intent-to-treat (ITT)	All randomized patients (primary analysis efficacy)
Safety	All patients who received any amount of IMP (vosaroxin, placebo, or cytarabine)
ECG/PK Substudy	All patients enrolled in the ECG and PK substudy who received at least one dose of study medication or placebo and had at least one analyzable baseline ECG and one analyzable post-treatment ECG. For the PK-PD analysis, a time-matched plasma concentration was necessary.
Patients ≥ 60 years (ad hoc population)	Subgroup analyses in all randomized patients ≥ 60 years

Primary analysis

The primary efficacy endpoint analysis was based on the Log-Rank test. Overall survival was censored at the earlier of the cut-off date for analysis or the last date known to be alive for patients not known to have died. The primary analysis of OS did not censor patients for subsequent transplantation or for any subsequent non-protocol AML therapy. Kaplan-Meier methods will be used to estimate OS for each treatment group. Estimates of median survival will be provided along with 95% CIs. The hazard ratio and 95% CI estimates will be generated using Cox proportional hazards modelling.

A stratified Log-Rank test by the stratification factors used at randomisation was used as supportive evidence of efficacy. Additional Log-Rank tests will be performed within each of the strata defined at randomisation and for the 2 first relapsed disease strata combined.

Sensitivity analyses were performed to assess both the effect of subsequent transplantation and that of any subsequent non-protocol AML therapy (including conditioning regimens for transplantation) on OS.

Subgroup analyses

Planned analyses by the stratification variables and in the 2 first relapse disease strata combined (early + late first relapse) were to be performed. No analyses were planned based on baseline cytogenetics/molecular abnormalities or type of AML (de novo or secondary), however, these analyses were performed post-hoc.

Secondary analyses

A point estimate of the CR rate was calculated for each arm as the percentage of patients with a CR. Patients who died before a response assessment was made were assigned to the treatment failure category. The CR rate (95% CI by Clopper-Pearson method) was compared between arms using a Chi-squared test. In addition, analysis using a Cochran-Mantel-Haenszel test stratified by the stratification factors and 2 first relapsed disease strata combined was performed. A 95% confidence interval for the difference in CR rates between treatment arms was calculated using the normal approximation to the binomial distribution.

Tertiary analyses

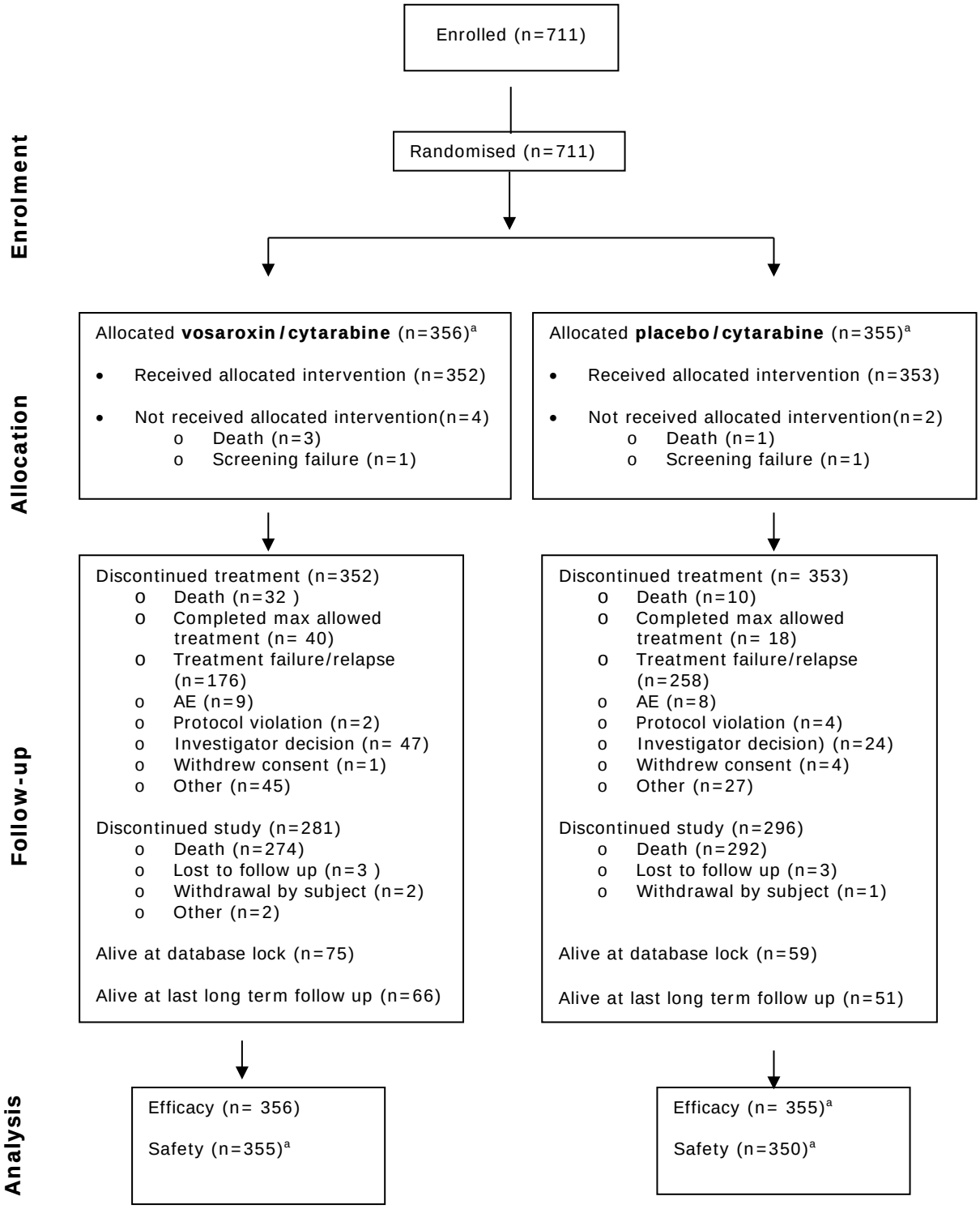
Analyses of CR + CRp rate, combined CR rate and the OR rate used the same methods as the analysis of the CR. Log-Rank tests were used to compare EFS and LFS. Supportive analyses were conducted using stratified log-rank tests. Descriptive analyses were performed using Kaplan-Meier methods. For LFS, the analyses were performed both with and without censoring for both subsequent transplantation and any non-protocol therapy.

- **Results**

First patient randomized: 17/12/2010

Date of database lock for primary analysis: 26/09/2014

Cut-off date for long-term follow-up: 29/04/2015 (long-term follow up is ongoing)



[a] Three patients randomized to placebo/cytarabine received vosaroxin in error and are included in the placebo arm for efficacy analysis and in vosaroxin arm for safety analysis. One patient randomized to vosaroxin/cytarabine received 6 doses of vosaroxin but received 1 dose of placebo in error. This patient is included in the vosaroxin/cytarabine arm in both the ITT population and the Safety population

The primary reason for treatment discontinuation was treatment failure/relapse (50.0% vosaroxin vs 73.1% placebo) and for study discontinuation was death (77.0% vosaroxin vs 82.3% placebo). Full details on reasons/timings of withdrawals have not been provided.

At the time of database lock for the primary analysis, 134 (18.8%) of the 711 randomized patients were alive.

At the time of last long-term follow-up (29/4/2015) on submission of the MAA, 117 (16.5%) of the 711 randomized patients were alive and being followed.

The study was conducted at 101 sites in the United States, Europe, Canada, Australia, New Zealand, and South Korea. A total of 41% of the patients came from EU.

Protocol amendments

The original protocol included one addendum made prior to first patient enrolment and four amendments. The original SAP (dated 10 November 2010) was amended one time prior to the interim analysis. The amendments were of no relevant impact for efficacy assessment.

Protocol compliance

The blind was not broken for any patient.

Randomization errors (4 patients), 307 violations in 173 patients and 1535 deviations in 477 patients were identified. The majority of violations/deviations concerned medication errors/infusion times.

Violations were mainly in the areas of “inclusions/exclusion criteria”, “regulatory” and “study drug”. The frequency of inclusion/exclusion criteria violations was low with 5.2% of patients affected. The majority of the regulatory violations involved informed consent forms and did not directly involve the assessment of efficacy or safety. The most common protocol deviations were related to missing procedures or tests.

Protocol violations and deviations did not affect the ability to assess the safety or efficacy in the overall patient population.

GCP

According to the applicant the study was conducted in compliance with Good Clinical Practice (GCP).

There was one GCP inspection conducted at the Vancouver site in August 2013 and the outcome confirmed the site activities were in line with regulatory principles. A routine GCP inspection was requested by CHMP on 9th February 2016. No specific concerns had been identified but in line with GCP Inspection Policy for centralised applications, due to the indication in AML, the adaptive design of pivotal study and that no inspections have been conducted by an EU inspectorate, compliance with GCP should be verified on pivotal study VOS-AML-301.

The inspection took place in April 2016 at the Sunesis Pharmaceuticals Inc site in South San Francisco (US) and the GCP report is dated 10th May 2016. No critical findings were identified and there were 4 major and 11 minor findings reported. It is anticipated that these findings are unlikely to have had an impact on the quality of the data

- **Baseline data**

Demographics, stratification factors and baseline disease characteristics are summarised in tables below. The majority of subjects were male (55.4%) and white (69.6%), with a mean age of 60.6 years). The overall characteristics of the patients were similar between the treatment arms.

Table 1. Demographics and Baseline BSA (ITT Population)

	Vosaroxin/Cytarabine N = 356	**Placebo/Cytarabine N =355**	**Total N = 711**
Age (years)			
Mean (SD)	61 (11.51)	60.2 (12.49)	60.6 (12.01)
Median	64.0	63.0	63.0
Min, Max	20, 80	18, 82	18, 82
Sex, n (%)[a]			
Male	202 (56.7)	192 (54.1)	394 (55.4)
Female	154 (43.3)	163 (45.9)	317 (44.6)
Ethnicity, n (%)[a]			
Hispanic or Latino	9 (2.5)	15 (4.2)	24 (3.4)
Not Hispanic or Latino	193 (54.2)	174 (49.0)	367 (51.6)
Not applicable (non-US site)	154 (43.3)	166 (46.8)	320 (45.0)
Race			
Asian	20 (5.6)	18 (5.1)	38 (5.3)
Black or African American	21 (5.9)	11 (3.1)	32 (4.5)
White	253 (71.1)	242 (68.2)	495 (69.6)
Multiple	0	3 (0.8)	3 (0.4)
Other	4 (1.1)	7 (2.0)	11 (1.5)
Not reported	58 (16.3)	74 (20.8)	132 (18.6)
Min, Max	1.4, 2.6	1.2, 2.6	1.2, 2.6
Body surface area (m2)			
N	352	353	705
Mean (SD)	1.9 (0.24)	1.9 (0.26)	1.9 (0.25)
Median	1.9	1.9	1.9
Min, Max	1.4, 2.6	1.2, 2.6	1.2, 2.6

Approximately 63% of patients were ≥ 60 years of age, 45% of patients enrolled were from US and 55% came from outside the US. The largest percentage of patients in both arms was refractory AML (~42%), followed by early relapse (36%), and late relapse (22%). The treatment arms were balanced across the stratification factors.

Over half patients had WHO AML classification of "AML not otherwise specified" and over half had "intermediate" disease cytogenetics based on National Comprehensive Cancer Network (NCCN) guidelines. The median time from AML diagnosis to randomization was 8.3 months and most patients had an ECOG score of 0 or 1 at baseline.

Table 2. Stratification Factors and Baseline Disease Characteristics (ITT Population)

	Vosaroxin/Cytarabine N = 356 n (%)	**Placebo/Cytarabine N = 355 n (%)**	**Total N = 711 n (%)**
Stratification Parameters			
Age			
< 60 years	130 (36.5)	130 (36.6)	260 (36.6)
≥ 60 years	226 (63.5)	225 (63.4)	451 (63.4)
Disease status			
Refractory	152 (42.7)	149 (42.0)	301 (42.3)
First CR or CRp ≥ 90 days and < 12 months	127 (35.7)	129 (36.3)	256 (36.0)
First CR or CRp ≥ 12 months and < 12 months	77 (21.6)	77 (21.7)	154 (21.7)
Geographic location			
Within the US	161 (45.2)	159 (44.8)	320 (45.0)
Outside the US	195 (54.8)	196 (55.2)	391 (55.0)
Other Baseline Disease Characteristics			
ECOG Performance Status			
0 (normal activity)	156 (44.1)	143 (40.5)	299 (42.3)
1 (symptoms but ambulatory)	158 (44.6)	162 (45.9)	320 (45.3)
2 (in bed < 50% of time)	40 (11.3)	48 (13.6)	88 (12.4)
Missing	2	2	4
Initial WHO Classification of AML			
AML with recurrent genetic abnormalities	54 (15.2)	71 (20.0)	125 (17.6)
Myeloid sarcoma	2 (0.6)	1 (0.3)	3 (0.4)
Therapy-related myeloid neoplasm	9 (2.5)	10 (2.8)	19 (2.7)
AML with myelodysplasia-related changes	103 (28.9)	93 (26.2)	196 (27.6)
AML not otherwise specified	188 (52.8)	180 (50.7)	368 (51.8)
Cytogenetics by National Comprehensive Cancer Network			
n	240	239	479
Favorable	7 (2.9)	9 (3.8)	16 (3.3)
Intermediate	175 (72.9)	155 (64.9)	330 (68.9)
Unfavorable	58 (24.2)	75 (31.4)	133 (27.8)
Missing	116	116	232

Table 2. Stratification Factors and Baseline Disease Characteristics (ITT Population)

	Vosaroxin/Cytarabine N = 356 n (%)	**Placebo/Cytarabine N = 355 n (%)**	**Total N = 711 n (%)**
Time from AML diagnosis to randomization (months)			
n	347	347	694
Mean (SD)	9.0 (6.95)	9.1 (7.23)	9.1 (7.08)
Median	8.4	8.2	8.3
Min, Max	0.8, 32.7	0.9, 42.7	0.8, 42.7
Missing	9	8	17
Patients with molecular abnormalities[a]			
NPM1			
N	75	75	150
Mutated	22 (29.3)	25 (33.3)	47 (31.3)
Wild type	53 (70.7)	50 (66.7)	103 (68.7)
FLT3			
N	83	82	165
Mutated	17 (20.5)	20 (24.4)	37 (22.4)
Wild type	66 (79.5)	62 (75.6)	128 (77.6)

The ITT is defined as all patients who were randomized. Percentages are based on the number of patients randomized.

[a]Percentages are based on the number of patients with molecular abnormalities data available. AML, acute myeloid leukemia; CR, complete remission; CRp, complete remission with incomplete platelet recovery; ECOG, Eastern Cooperative Oncology Group; FLT3, Fms-like tyrosine kinase 3; ITT, intent-to-treat; Max, maximum; Min, minimum; NPM1, nucleophosmin; SD, standard deviation; US, United States; WHO, World Health Organization

In the ITT population 75.0% had only one induction cycle of a previous treatment for AML and over half of patients (58.6%) had one or more consolidation/maintenance cycles. Most patients did not have a transplant conditioning regimen (91.0%). There were no clinically meaningful differences between the treatment arms.

Table 3. Prior Treatments for Acute Myeloid Leukemia by Treatment (ITT Population)

	Vosaroxin / Cytarabine N = 356 n (%)	Placebo / Cytarabine N = 355 n (%)	Total N = 711 n (%)
Induction cycles per patient			
1	274 (77.0)	259 (73.0)	533 (75.0)
2	82 (23.0)	95 (26.8)	177 (24.9)
> 2	0	1 (0.3)	1 (0.1)
Consolidation / maintenance cycles per patient			
0	150 (42.1)	144 (40.6)	294 (41.4)
1	54 (15.2)	45 (12.7)	99 (13.9)
2	65 (18.3)	72 (20.3)	137 (19.3)
> 2	87 (24.4)	94 (26.5)	181 (25.5)
Transplant conditioning regimen cycles per patient			
0	323 (90.7)	324 (91.3)	647 (91.0)
1	33 (9.3)	31 (8.7)	64 (9.0)
2	0	0	0
> 2	0	0	0
Other cycles per patient			
1	4 (1.1)	1 (0.3)	5 (0.7)
2	0	0	0
> 2	0	0	0

Regimens administered intrathecal have been omitted from the count.

Concomitant medications

Drugs for GI tract (mainly antiemetics/nausea, laxatives, antidiarrhoea, anti-acids, minerals, stomatological preparations) and systemic anti-infectives were used in nearly all patients (99.7%). Muskuloskeletal drugs (primarily anti-gout) were used in 72% of patients.

The profile of use of concomitant medications during the study was similar between treatment arms with the exception of the following (vosaroxin/cytarabine vs placebo/cytarabine): antivirals for systemic use (85.1% vs 73.7%), blood substitutes and perfusion solutions (79.4% vs 62.6%), diuretics (57.2% vs 48.9%), and corticosteroids for systemic use (62.8% vs 54.3%).

Treatment exposure:

Most patients received one induction treatment only, i.e. 55.1% versus 67.9% for patients on vosaroxin/cytarabine and placebo/cytarabine, respectively. About 17% received two induction cycles (16.9% on vosaroxin/cytarabine and 17.2% on placebo/cytarabine), and 12.9% on vosaroxin/cytarabine received one induction and one consolidation treatment compared to 5.1% on placebo/cytarabine (see also Safety section). A similar pattern was observed for patients ≥60 years, i.e. 54.0% on vosaroxin/cytarabine and 68.9% on placebo/cytarabine had only one induction treatment.

- **Interim analysis**

At the pre-specified interim analysis (10th September 2012) median OS was 8.3 months (95% CI, 6.6-10.1 months) for vosaroxin/cytarabine versus 6.0 months (95% CI, 4.3-7.1 months) for placebo/cytarabine (HR = 0.76, unstratified log-rank one-sided p-value = 0.0378).

Neither the efficacy nor the futility boundaries were crossed at interim and the DSMB recommended that the target number of events be increased by 50% (to 562 events in 675 patients) and which allowing for a 5% dropout rate, was increased to 712 patients.

Primary analyses

OS

The primary analysis of OS (unstratified log-rank test) reported a median OS for patients treated with vosaroxin/cytarabine of 7.5 months vs 6.1 months control (HR = 0.87, one sided p = 0.0305) that was below the hurdle for statistical significance (one-sided p-value of 0.0247), see Figure 2. This means that formally the study has failed to reject its null-hypothesis and that results from additional analyses must be interpreted with caution.

A pre-specified supportive stratified log-rank test reported a HR 0.83 with one sided p value 0.0121.As there were no missing events in any interim stratum the Applicant claims the more appropriate analysis is the stratified one.

Table 4. Overall Survival by Treatment (ITT Population)

	Vosaroxin/Cytarabine N = 356	**Placebo/Cytarabine N = 355**	**Total N = 711**
Kaplan-Meier estimated duration of OS (months)			
Events (%)	272 (76.4)	290 (81.7)	562 (79.0)
Censored (%)	84 (23.6)	65 (18.3)	149 (21.0)
25th percentile (95% CI)	2.7 (2.1, 3.3)	2.5 (2.0, 3.0)	2.6 (2.1, 3.0)
Median (95% CI)	7.5 (6.4, 8.5)	6.1 (5.2, 7.1)	6.7 (6.1, 7.6)
75th percentile (95% CI)	19.9 (15.5, 24.3)	14.0 (11.8, 18.2)	16.6 (13.8, 19.9)
Min, Max	0.1, 43.0	0.3, 37.3	0.1, 43.0
Primary Analysis: Adjusted log-rank test[a] for comparison of OS between treatment arms: **one-sided**			Z = -1.87 p = 0.0305
Hazard ratio[b] (95% CI)			HR = 0.87 (0.73, 1.02)
Adjusted stratified[c] log-rank test[a] for comparison of OS between treatment arms: **one-sided**			Z = -2.26 p = 0.0121
Stratified[c] hazard ratio (95% CI)			HR = 0.83 (0.70, 0.98)
Kaplan-Meier survival rate (95% CI)			
6 months	58.6 (53.3, 63.5)	50.8 (45.5, 55.9)	54.7 (50.9, 58.3)
12 months	34.8 (29.9, 39.8)	29.6 (24.9, 34.5)	32.2 (28.8, 35.7)
18 months	26.1 (21.5, 31.0)	21.2 (16.9, 25.7)	23.7 (20.5, 27.0)
24 months	20.2 (15.6, 25.1)	16.4 (12.5, 20.8)	18.2 (15.2, 21.5)

Notes: Maximum observations are censored.

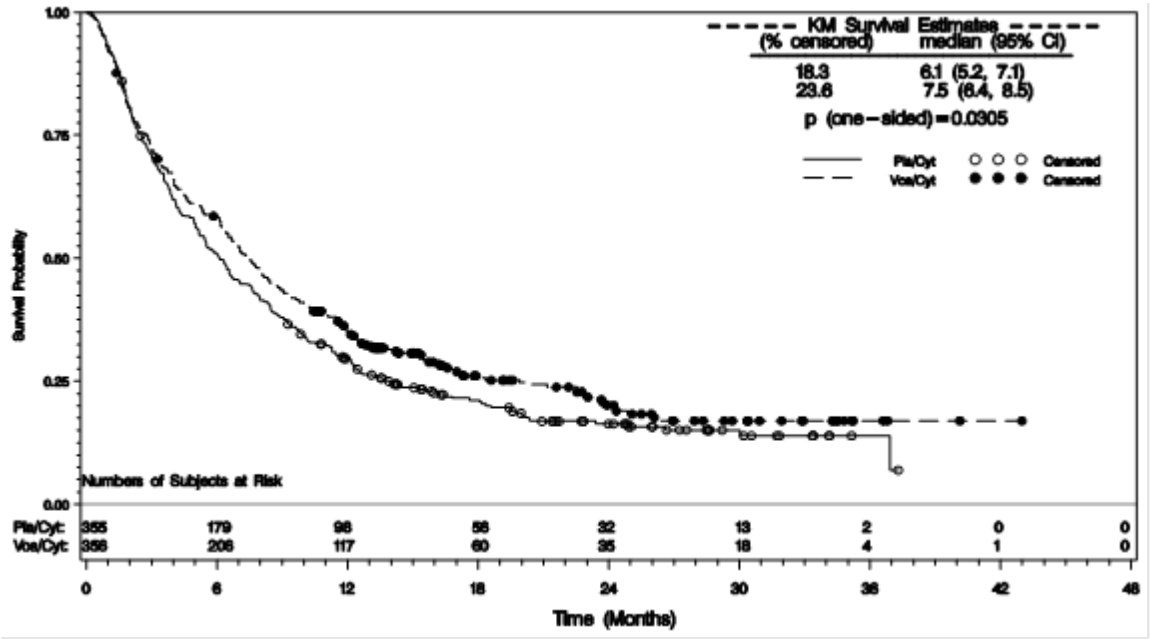
One month is assumed to be 30.42 days. The nominal one-sided p-value for statistical significance (0.024727) has been adjusted to account for the alpha spent at the interim analysis for efficacy performed during the study.

a Test statistics are adjusted using the methodology of Cui, Hung, and Wang (1999) to account for the pre-specified sample size adjustment at the interim.

b Unadjusted Cox Proportional Hazards model was used.

c Stratification variables used in the model are the randomization strata: disease status (refractory, first relapse with duration of first CR or CRp ≥ 90 days and < 12 months, or first relapse with duration of first CR or CRp ≥ 12 months and ≤ 24 months), age (<60 years or ≥ 60 years), and geographic location (US or outside US).

Figure 2 Overall Survival by Treatment (ITT Population)



Note: Log rank adjusted p value using Cui, Hung, and Wang method (Cui 1999).

In the original submission an updated analysis at the time of last- follow-up (29/4/2015), 9 months after the primary analysis, with 117 (16.5%) of the 711 randomized patients alive showed similar results to the primary analysis, with median OS of 7.5 months versus 6.1 months, respectively, for vosaroxin/cytarabine versus placebo/cytarabine and an HR of 0.87 (unstratified one-sided p = 0.0296; stratified one-sided p = 0.0125).

Results from the sensitivity analyses are consistent with the primary analysis.

Median OS in patients censored for transplantation was prolonged in the vosaroxin arm compared to the control (6.7 months vs 5.3 months; HR = 0.81, unstratified one sided p = 0.0122).

Among patients censored for subsequent AML therapy including transplantation, the median OS was prolonged in the vosaroxin arm compared to the control (median 8.4 months versus 6.3 month, HR = 0.79, unstratified one-sided p = 0.0488). These analyses demonstrate improved survival of patients treated with vosaroxin/cytarabine compared to those treated with placebo/cytarabine up to the point of transplantation.

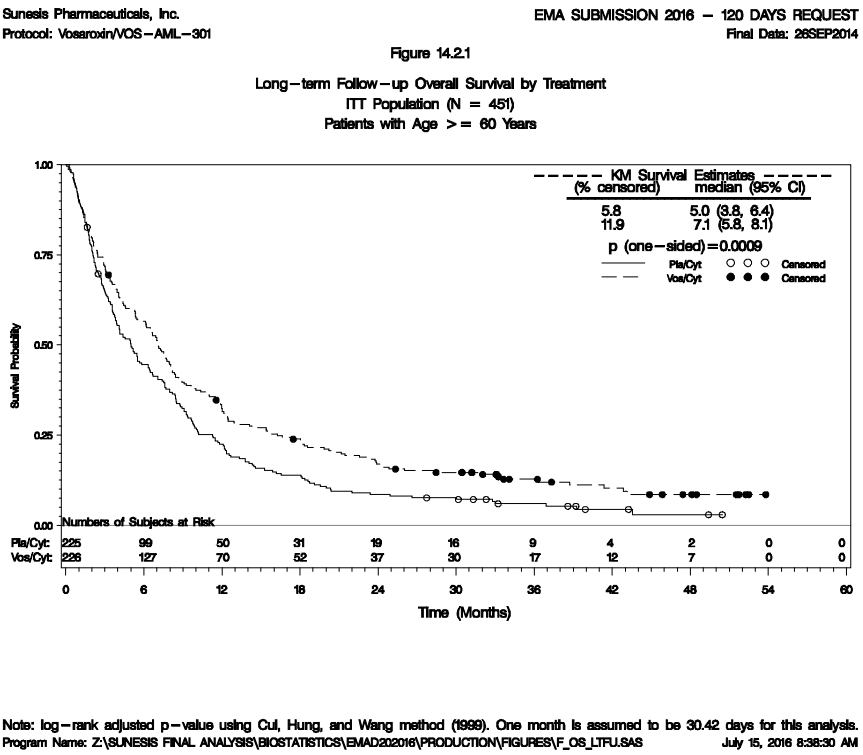
OS update on follow-up (January 2016)

As of 22 January 2016, 83 patients were alive in follow up including 46/356 (12.9%) in the vosaroxin/cy arm and 37/355 (10.4%) in the placebo/cy arm and for patients ≥ 60 years 23/226 (10.2%) were alive in the vosaroxin/cy arm and 10/225 (4.4%) in the placebo/cy arm.

In patients ≥ 60 years, the separation of the OS curves was maintained through 48 months (Fig 4). After 24 and 36 months, approximately twice as many patients were alive in the vosaroxin/cy arm compared with the placebo/cy arm (37 versus 19, respectively at 24 months and 17 versus 9, respectively, at 36 months). The OS benefit associated with vosaroxin/cy was durable, as demonstrated by the continued separation of the survival curves beyond 48 months in patients ≥ 60 years and beyond 36 months for the total VALOR ITT population (Fig 4).

The favorable HR for vosaroxin/cytarabine compared with placebo/cytarabine observed in the original analysis was confirmed with long-term follow-up.

Figure 4. VALOR Overall Survival Update (January 2016): Patients ≥ 60 years of age



Note: p = 0.0017 (two sided)

Table 5. Overall Survival Results in VALOR January 2016 Update, ITT Population

	All Patients		Patients ≥ 60 Years of Age	
	Vos/Cyt N = 356	**Pla/Cyt N = 355**	**Vos/Cyt N = 226**	**Pla/Cyt N = 225**
Median OS (95% CI) (months)	7.5 (6.4, 8.5)	6.1 (5.2, 7.1)	7.1 (5.8, 8.1)	5.0 (3.8, 6.4)
Log-rank test[a] two-sided p-value	p = 0.0797		p = 0.0017	
Stratified[c] log-rank test[a] two-sided p-value	p = 0.0367		p = 0.0023	
Hazard ratio[b] (95% CI)	0.88 (0.75, 1.03)		0.75 (0.62, 0.91)	
Stratified[c] Hazard ratio (95% CI)	0.85 (0.72, 1.00)		0.76 (0.62, 0.92)	

One month is assumed to be 30.42 days. The ITT population consisted of all patients randomized.

CI, confidence interval; CR, complete remission; CRp, complete remission with incomplete platelet recovery; Cyt, cytarabine; ITT, intent-to-treat; OS, overall survival; Pla, placebo; US, United States; Vos, vosaroxin.

a Test statistics are adjusted using the methodology of Cui 1999 to account for the pre-specified sample size adjustment at the interim.

b Unadjusted Cox Proportional Hazards model was used.

c Stratification variables used in the model are the randomization strata: disease status (refractory, first relapse with duration of first CR or CRp ≥ 90 days and < 12 months, or first relapse with duration of first CR or CRp ≥ 12 months and ≤ 24 months), age (< 60 years or ≥ 60 years) – not used for the ≥ 60 years analyses, and geographic location (US or outside US).

A statistical test for interaction to assess the heterogeneity of treatment effect in the randomization strata subgroups was conducted with data at the time of unblinding and after this long term follow up. At the time of unblinding, a difference in treatment effect by age group (≥ 60 years versus < 60 years) was detected (p = 0.0501) with a larger treatment effect observed in the >60 patients. With this long-term follow-up, the results of the primary analysis have been confirmed with the update of the data. Interaction tests by the other prespecified strata (disease status and geographic location) did not reveal any differences in treatment effect between subgroups.

Hazard Ratio Estimates for Overall Survival by Strata in VALOR ITT Population, Final Analysis and Long-term Follow-up

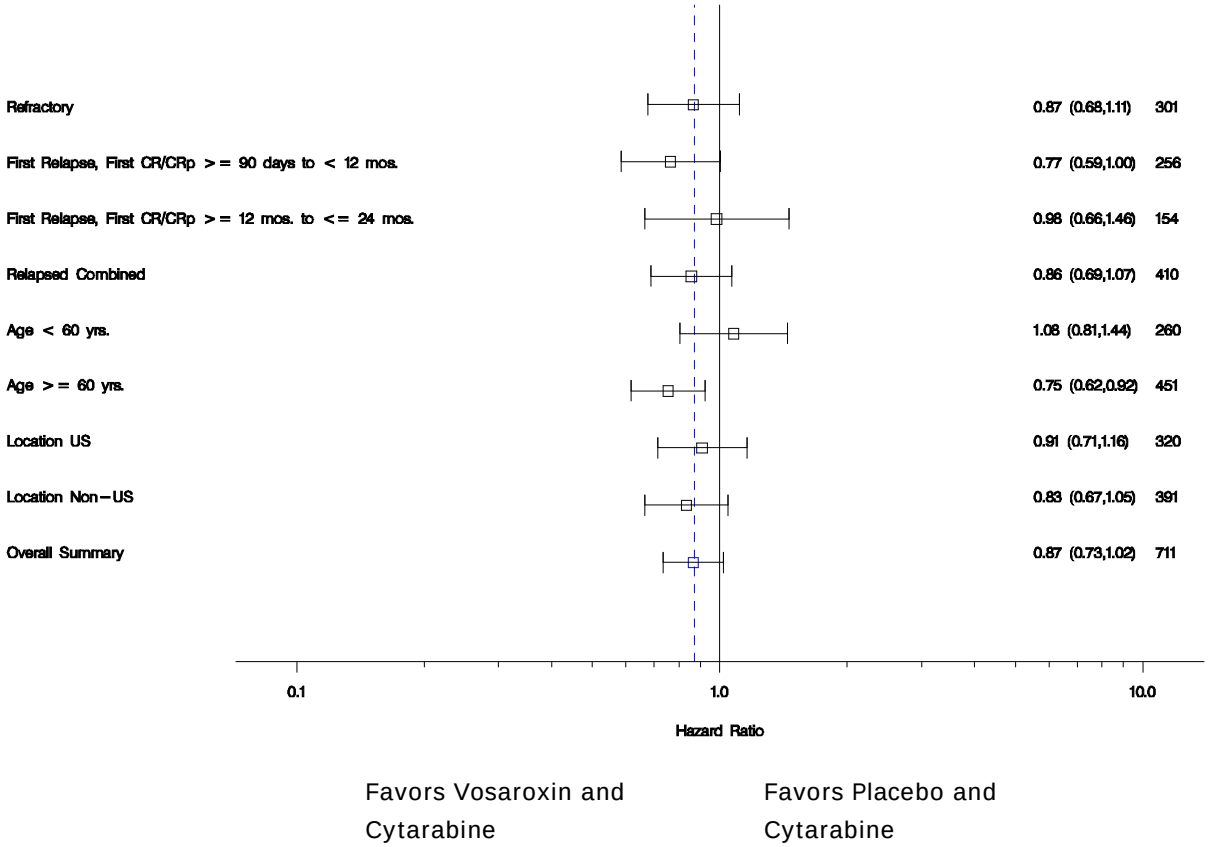
	Final Analysis			Additional Follow-up		
	n	Hazard ratio (95% CI)	p-value for interaction test	n	Hazard ratio (95% CI)	p-value for interaction test
Disease Status						
Refractory	301	0.87 (0.68, 1.11)	0.5699	301	0.90 (0.71, 1.15)	0.4150
Early Relapsed	256	0.77 (0.59, 1.00)		256	0.76 (0.59, 1.00)	
Late Relapsed	154	0.98 (0.66, 1.46)		154	1.01 (0.702, 1.45)	
Age Group						
<60 years	260	1.08 (0.81, 1.44)	0.0501	260	1.10 (0.83, 1.46)	0.0296
≥60 years	451	0.75 (0.62, 0.92)		451	0.75 (0.62, 0.91)	
Geographic Region						
US	320	0.91 (0.71, 1.16)	0.5486	320	0.91 (0.72, 1.15)	0.6818
Non-US	391	0.83 (0.67, 1.05)		391	0.87 (0.70, 1.08)	

The ITT population consisted of all patients randomized. Hazard ratio and 95% CI for overall survival using PHREG model Failure time*censor = treatment group. P-value for interaction test; obtained the difference of likelihood ratio chi square from failure time model (PHREG) using models with and without interaction terms (strata treatment) vs (strata treatment strata*treatment). P-value = 1-cdfchisq(chisquare,x,df). CI, confidence interval; ITT, intent-to-treat; US, United States

- **Subgroup analysis**

The survival analyses in subgroups defined by the stratification factors favoured the vosaroxin arm, with the exception of patients < 60 years of age. A statistically significant *OS* benefit was observed in patients ≥ 60 years of age and those with early relapse (≥ 90 days to < 12 months).

Fig 6 Hazard Ratio Estimates for Overall Survival by Strata (ITT Population)



Note: The vertical dashed line indicates the overall hazard ratio.

Age-defined subgroup (patients < 60 years and patients ≥ 60 years)

Patients < 60 years (n = 260) demonstrated a median OS of 9.1 months in the vosaroxin/cytarabine arm versus 7.9 months in the placebo/cytarabine arm (HR = 1.08, one-sided p = 0.70). Among patients ≥ 60 years (n = 451), the median OS was 7.1 months in the vosaroxin/ cytarabine arm compared with 5.0 months in the placebo/ cytarabine arm (HR = 0.75, one-sided p = 0.0015)and a supportive stratified analysis also demonstrated significance (HR = 0.74, one-sided log-rank p = 0.0009).

In a sensitivity analysis, the improvement in OS with the addition of vosaroxin remained significant in patients ≥ 60 years when censored at the time of subsequent transplantation (OS median 6.7 months versus 5.0 months, HR = 0.75, one-sided p = 0.0043) or when censored at the time of any post-treatment therapy (2.5-month improvement in OS with the addition of vosaroxin; HR = 0.72, unstratified one-sided p = 0.0187).

As an explanation for the lack of effect in patients younger than 60 years, the Applicant argued that these patients apparently had a more cytarabine-sensitive leukaemia, which may have affected OS in a positive way in both arms. This notion fits with the observation that the placebo arm had better OS results than expected (i.e. 6.1 months while 5.0 months was expected).

It is noteworthy that the difference in OS for the age-driven subgroup is larger (and statistically significant) due to the fact that the results in the comparator arm were worse as compared to those observed in the ITT, for reference, 5.0 months in the patients ≥ 60 years and 6.1 months for the ITT.

Disease status

The vosaroxin arm showed an increase in OS versus placebo arm in all disease status subgroups but median OS was significantly longer with vosaroxin in patients ≥ 60 years with refractory (2.9-month improvement) or early relapsed disease (2.6-month improvement). No significant difference was observed in patients ≥ 60 years of age with late relapsed AML (median 9.2 versus 9.8 months). The improvement in OS with vosaroxin in the combined subgroup of patients with refractory or early relapsed disease was 2.6 months (median OS 6.5 months vosaroxin vs 3.9 months placebo; HR 0.69[0.55, 0.86].

Table 2.5-4: Overall Survival in VALOR by Baseline Disease Status, ITT Population

Kaplan-Meier estimates for overall survival	VALOR All Patients		VALOR Patients ≥ 60 Years of Age	
	Vos/Cyt	Pla/Cyt	Vos/Cyt	Pla/Cyt
Refractory	**N = 152**	**N = 149**	**N = 105**	**N = 105**
Events (%)	121 (79.6)	126 (84.6)	86 (81.9)	95 (90.5)
Censored (%)	31 (20.4)	23 (15.4)	19 (18.1)	10 (9.5)
Median duration of OS (95% confidence interval, CI) (months)	6.7 (4.2, 7.8)	5.0 (3.6, 6.3)	6.7 (3.9, 8.1)	3.8 (3.0, 5.5)
Log-rank test, 1-sided[a]	Z = -1.21; p = 0.1134		Z = -2.09; p = 0.0182	
Hazard ratio (95% CI)[b]	0.87 (0.68, 1.11)		0.73 (0.55, 0.98)	
Early Relapse	**N = 127**	**N = 129**	**N = 77**	**N = 77**
Events (%)	102 (80.3)	113 (87.6)	62 (80.5)	72 (93.5)
Censored (%)	25 (19.7)	16 (12.4)	15 (19.5)	5 (6.5)
Median duration of OS (95% CI) (months)	6.7 (4.6, 8.7)	5.2 (3.8, 6.6)	6.5 (4.0, 8.7)	3.9 (2.9, 6.3)
Log-rank test, one-sided[a]	Z = -2.07; p = 0.0194		Z = -2.81; p = 0.0025	
Hazard ratio (95% CI)[b]	0.77 (0.59, 1.00)		0.61 (0.43, 0.86)	
Late Relapsed	**N = 77**	**N = 77**	**N = 44**	**N = 43**
Events (%)	49 (63.6)	51 (66.2)	33 (75.0)	34 (79.1)
Censored (%)	28 (36.4)	26 (33.8)	11 (25.0)	9 (20.9)
Median duration of OS (95% CI) (months)	14.1 (7.9, 22.6)	12.3 (9.1, 18.4)	9.2 (7.0, 17.3)	9.8 (7.6, 14.3)
Log-rank test, one-sided[a]	Z = -0.05; p = 0.4807		Z = 0.23; p = 0.5920	
Hazard ratio (95% CI)[b]	0.98 (0.66, 1.46)		1.06 (0.65, 1.72)	

Source: VALOR Table 14.2.1.4 and Table 2.7.3-11

Notes: Early relapsed is defined as first relapse with duration of first CR or CRp ≥ 90 days and < 12 months. Late relapsed is defined as first relapse with duration of first CR or CRp ≥ 12 months and ≤ 24 months. One month is assumed to be 30.42 days. The ITT population consists of all patients randomized

Abbreviations: CI, confidence interval; Cyt, cytarabine; OS, overall survival; Pla, placebo; Vos, vosaroxin

a The VALOR all patients analyses in these subgroups were pre-specified in the SAP to be adjusted using the methodology of Cui 1999 to account for the pre-specified sample size adjustment at the interim. The results for the VALOR patients ≥ 60 years of age are unadjusted

b Unadjusted Cox Proportional Hazards model is used.

Overall survival by Baseline Cytogenetics

Cytogenetic risk at baseline was available for approximately two-thirds of the VALOR ITT population and two-thirds of the ≥ 60 years population and the majority of patients in each arm had intermediate cytogenetic risk for both the ITT (73% vosaroxin/65% placebo) and the ≥ 60 years population(73% vosaroxin/67% placebo). The patients classified according to cytogenetic risk at baseline were rather balanced between the 2 treatment arms in both the ITT and the subgroup of patients 60 year and older. The number of patients with favorable cytogenetics in both study populations is too small for conclusions to be drawn (7 patients vosaroxin/9 patients placebo).

A greater improvement in OS was observed for vosaroxin/cy compared with placebo/cy in both the intermediate (median OS 8.3 months vosaroxin vs 7.1 months placebo; HR 0.88 [0.69, 1.13], p=0.299) and unfavorable(median OS 5.0 months vosaroxin vs 3.8 months placebo; HR 0.79 [0.55, 1.14], p=0.021) risk groups for both the ITT population. The same pattern was observed for the ≥ 60 years populations. In the ≥ 60 years population, the greatest improvement was found in the unfavorable risk group(median OS 5.9 months vosaroxin vs 2.8 months placebo; HR 0.49 [0.31, 0.80], p=0.0032) compared to the intermediate group (median OS 7.8 months vosaroxin vs 6.0 months placebo; HR 0.82 [0.61, 1.10], p=0.19).

Overall Survival by Molecular Characteristics at Baseline

Molecular characteristics were available for only approximately one-fifth of the patients and wild-type molecular characteristics were more common than mutated for both NPM1 and FLT3. No information was provided on the presence of combined/complex molecular abnormalities.

Baseline Molecular Abnormalities Data in the VALOR Study, ITT Population

Patients with molecular abnormalities, n (%)	All Patients		Patients ≥ 60 Years of Age	
	Vos/Cyt N = 356	Pla/Cyt N = 355	Vos/Cyt N = 226	Pla/Cyt N = 225
NPM1				
n	75	75	47	45
Mutated	22 (29.3)	25 (33.3)	15 (31.9)	15 (33.3)
Wild type	53 (70.7)	50 (66.7)	32 (68.1)	30 (66.7)
FLT3				
n	83	82	50	48
Mutated	17 (20.5)	20 (24.4)	10 (20.0)	15 (31.3)
Wild type	66 (79.5)	62 (75.6)	40 (80.0)	33 (68.8)

Favourable results of OS by molecular abnormalities for vosaroxin arm for those patients with data in the ITT population was reported for mutated NPM1 (HR 0.94), mutated FLT3 (HR 0.47) and wild type NPM1 (HR 0.97). The HR for patients with wild type FLT3 was at 1.09.

Overall survival by baseline type of AML

In the ITT population, approximately half of patients had a WHO AML classification of AML not otherwise specified, 28% had AML with myelodysplasia-related changes, 18% had AML with recurrent genetic abnormalities, and 3% had therapy-related myeloid neoplasm; baseline WHO classification at diagnosis was distributed similarly in patients ≥ 60 years of age.

The majority of patients had primary de novo AML and the results were in line with those of the overall population. The number of patients with secondary AML or prior cancer were too limited to draw firm conclusions on the results.

Overall Survival by Primary versus Secondary AML (ITT Population and Patients ≥ 60 Years)

ITT Population						
			Secondary AML[a]			
	Primary AML		**AHD (including prior MDS)**		**Prior Cancer**	
	Vos/cyt (n=298)	Pla/cyt (n=287)	Vos/cyt (n=38)	Pla/cyt (n=37)	Vos/cyt (n=24)	Pla/cyt (n=43)
Median OS, months (95% CI)	7.9 (6.9, 9.2)	6.4 (5.5, 7.8)	3.6 (2.4, 4.6)	5.0 (2.4, 8.4)	8.9 (3.0, 24.9)	5.0 (3.9, 7.1)
Log-rank test p-value, two-sided	0.1168		0.6972		0.0691	
Stratified log-rank test p-value, two-sided[b]	0.0569		0.8888		0.1192	
Hazard ratio[c] (95% CI)	0.86 (0.72,1.04)		1.10 (0.67,1.80)		0.59 (0.33,1.05)	
Stratified hazard ratio[b] (95% CI)	0.83 (0.69,1.01)		1.04 (0.58,1.88)		0.59 (0.30,1.15)	
Patients ≥ 60 Years						
			Secondary AML[a]			
	Primary AML		**AHD (including prior MDS)**		**Prior Cancer**	
	Vos/cyt (n=183)	Pla/cyt (n=177)	Vos/cyt (n=26)	Pla/cyt (n=27)	Vos/cyt (n=19)	Pla/cyt (n=32)
Median OS, months (95% CI)	7.5 (6.5, 8.4)	5.0 (3.6, 6.5)	3.4 (1.9, 6.1)	5.3 (2.2, 8.5)	8.1 (2.0, 24.9)	4.9 (3.0, 7.1)
Log-rank test p-value, two-sided	0.0043		0.4642		0.0278	
Stratified log-rank test p-value, two-sided[b]	0.0050		0.6811		0.1550	
Hazard ratio[c] (95% CI)	0.72 (0.57, 0.90)		1.24 (0.70, 2.20)		0.48 (0.25, 0.94)	
Stratified hazard ratio[b] (95% CI)	0.72 (0.57, 0.91)		1.15 (0.58, 2.29)		0.59 (0.29, 1.23)	

Abbreviations: AHD, antecedent hematologic disease; CI, confidence interval, CR, complete remission; CRp, complete remission with incomplete platelet recovery; MDS, myelodysplastic syndrome; OS, overall survival; US, United States.

[a] 4 patients in the vosaroxin/cytarabine arm (2 patients ≥ 60 years) and 12 patients in the placebo/cytarabine arm (11 patients ≥ 60 years) had AHD and other prior cancer and are included in both categories.

[b] Stratification variables used in the model are the randomization strata: disease status (refractory, first relapse with duration of first CR or CRp >=90 days and <12 months, or first relapse with duration of first CR or CRp >=12 months and <=24 months), age (<60 years or >=60 years), and geographic location (US or outside US)

[c] Unadjusted Cox Proportional Hazards model is used.

CR

The secondary endpoint favoured vosaroxin arm (30.1% vs 16.3%) and achieved statistical significance (two sided p < 0.0001).

Table 5. Complete Remission Rate by Treatment (ITT Population)

	Vosaroxin/Cytarabine N = 356	**Placebo/Cytarabine N = 355**	**Total N = 711**
Complete remission			
n (%)[a]	107 (30.1)	58 (16.3)	165 (23.2)
95% CI[b]	25.3, 35.1	12.6, 20.6	20.1, 26.5
Difference in percentage	13.7		—
95% CI for difference[c]	7.6, 19.8		—
Chi-square	X^2 = 18.77 p < 0.0001		—
CMH test[d]	X^2 = 19.97 p < 0.0001		—

All p-values are two-sided.

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; CR, complete remission; CRp, complete remission with incomplete platelet recovery; ITT, intent-to-treat; US, United States

[a] n (%) represents the number and percentage of ITT patients.

[b] Exact 95% CI for percentage calculated by the Clopper-Pearson method.

[c] 95% CI for the difference in percentage between treatment arms was based on the normal approximation to the binomial distribution.

[d] The Cochran-Mantel-Haenszel test controlling for the randomization strata: disease status (refractory, first relapse with duration of first CR or CRp ≥ 90 days and < 12 months, or first relapse with duration of first CR or CRp ≥ 12 months and ≤ 24 months), age (< 60 years or ≥ 60 years), and geographic location (US or outside US).

The Applicant assessed the concordance between the investigator and CPARR with generally good agreement overall (94.7%), in particular with respect to no CR (74.5%).

The CR rates were significantly higher in the vosaroxin/cytarabine arm compared with the placebo in all stratification groups with the exception of patients < 60 years of age (6.2% difference between treatments; two-sided p = 0.24).

Table 6. Complete Remission Rate by Strata and Treatment (ITT Population)

	Vosaroxin/Cytarabine N = 356	Placebo/Cytarabine N = 355	Total N = 711
Refractory			
n (%)[a]	31 (20.4)	16 (10.7)	47 (15.6)
95% CI[b]	14.3, 27.7	6.3, 16.9	11.7, 20.2
Difference in percentage	9.7		—
95% CI for difference[c]	1.5, 17.8		—
Chi-square	X^2 = 5.32 p = 0.0210		—
First relapse: first CR or CRp ≥ 90 days and < 12 months			
n (%)[a]	35 (27.6)	16 (12.4)	51 (19.9)
95% CI[b]	20.0, 36.2	7.3, 19.4	15.2, 25.3
Difference in percentage	15.2		—
95% CI for difference[c]	5.5, 24.8		—
Chi-square	X^2 = 9.21 p = 0.0024		—
First relapse: first CR or CRp ≥ 12 months and ≤ 24 months			
n (%)[a]	41 (53.2)	26 (33.8)	67 (43.5)
95% CI[b]	41.5, 64.7	23.4, 45.4	35.5, 51.7
Difference in percentage	19.5		—
95% CI for difference[c]	4.1, 34.8		—
Chi-square	X^2 = 5.94 p = 0.0148		—
First relapse: combined			
n (%)[a]	76 (37.3)	42 (20.4)	118 (28.8)
95% CI[b]	30.6, 44.3	15.1, 26.5	24.4, 33.4
Difference in percentage	16.9		—
95% CI for difference[c]	8.2, 25.5		—
Chi-square	X^2 = 14.23 p = 0.0002		—
Age: < 60 years			
n (%)[a]	35 (26.9)	27 (20.8)	62 (23.8)
95% CI[b]	19.5, 35.4	14.2, 28.8	18.8, 29.5
Difference in percentage	6.2		—
95% CI for difference[c]	-4.2, 16.5		—
Chi-square	X^2 = 1.36 p = 0.2443		—
Age: ≥ 60 years			
n (%)[a]	72 (31.9)	31 (13.8)	103 (22.8)
95% CI[b]	25.8, 38.4	9.6, 19.0	19.0, 27.0
Difference in percentage	18.1		—
95% CI for difference[c]	10.5, 25.6		—
Chi-square	X^2 = 20.92 p < 0.0001		—

Table 6. Complete Remission Rate by Strata and Treatment (ITT Population)

	Vosaroxin/Cytarabine N = 356	**Placebo/Cytarabine N = 355**	**Total N = 711**
Location: US			
n (%)[a]	45 (28.0)	23 (14.5)	68 (21.3)
95% CI[b]	21.2, 35.6	9.4, 20.9	16.9, 26.1
Difference in percentage	13.5		—
95% CI for difference[c]	4.7, 22.3		—
Chi-square	X^2 = 8.69 p = 0.0032		—
Location: Outside US			
n (%)[a]	62 (31.8)	35 (17.9)	97 (24.8)
95% CI[b]	25.3, 38.8	12.8, 23.9	20.6, 29.4
Difference in percentage	13.9		—
95% CI for difference[c]	5.5, 22.4		—
Chi-square	X^2 = 10.18 p = 0.0014		—

Notes: All p-values are two-sided.

[a] Abbreviations: CI, confidence interval; CR, complete remission; CRp, complete remission with incomplete platelet recovery; ITT, intent-to-treat; US, United States

[e] n (%) represents the number and percentage of total patients in each respective stratum.

[f] Exact 95% CI for percentage calculated by the Clopper-Pearson method.

[g] 95% CI for the difference in percentage between treatment arms was based on the normal approximation to the binomial distribution.

Higher CR rates were associated with vosaroxin in patients ≥ 60 years irrespective of disease status.

Table 7 CR Rate by Treatment and by Disease status (Patients ≥ 60 years Age)

	Refractory		Early Relapsed		Late Relapsed		Refractory/Early Relapsed	
	Vos/Cyt N = 105	Pla/Cyt N = 105	Vos/Cyt N = 77	Pla/Cyt N = 77	Vos/Cyt N = 44	Pla/Cyt N = 43	Vos/Cyt N = 182	Pla/Cyt N = 182
Complete remission								
n (%)[a]	24 (22.9)	9 (8.6)	23 (29.9)	10 (13.0)	25 (56.8)	12 (27.9)	47 (25.8)	19 (10.4)
95% CI[b]	15.2-32.1	4.0-15.6	20.0-41.4	6.4-22.6	41.0-71.7	15.3-43.7	19.6-32.8	6.4-15.8
Difference in percentage	14.3		16.9		28.9		15.4	
95% CI for difference[c]	4.6-23.9		4.2-29.6		9.1-48.8		7.6-23.1	
Chi-square	$X^2 = 8.09$ p = 0.0045		$X^2 = 6.52$ p = 0.0107		$X^2 = 7.44$ p = 0.0064		$X^2 = 14.51$ p = 0.0001	
CMH test[d]	$X^2 = 8.05$ p = 0.0045		$X^2 = 6.44$ p = 0.0111		$X^2 = 7.37$ p =0.0066		$X^2 = 14.47$ p = 0.0001	

[b] Exact 95% CI for percentage calculated by the Clopper-Pearson method.

[c] 95% CI for the difference in percentage between treatment groups was based on the normal approximation to the binomial distribution.

[d] The Cochran-Mantel-Haenszel test controlling for the randomization strata: disease status (refractory, first relapse with duration of first CR or CRp ≥ 90 days and < 12 months) for the subset of combined refractory and early relapsed disease status, and geographic location (US or outside US) for all subsets.

The higher CR rate translated to a higher overall survival in the patient group with refractory and early disease. However, no improvement in overall survival was observed in the patient group with a late relapse, despite the higher CR rate.

Response rates

The overall and combined response rates were higher in the vosaroxin arm compared with placebo and differences between arms were statistically significant for all combined remission categories in favour of vosaroxin.

Table 8. Response Assessment by Treatment (ITT Population)

Number of Patients with:	Vosaroxin/Cytarabine N = 356	Placebo/Cytarabine N = 355	Total N = 711
Complete remission			
n (%)[a]	107 (30.1)	58 (16.3)	165 (23.2)
95% CI[b]	25.3, 35.1	12.6, 20.6	20.1, 26.5
Complete remission with incomplete platelet recovery (CRp)			
n (%)[a]	17 (4.8)	6 (1.7)	23 (3.2)
95% CI[b]	2.8, 7.5	0.6, 3.6	2.1, 4.8
Complete remission with incomplete recovery of platelets and neutrophils (CRi)			
n (%)[a]	8 (2.2)	2 (0.6)	10 (1.4)
95% CI[b]	1.0, 4.4	0.1, 2.0	0.7, 2.6
Partial remission			
n (%)[a]	3 (0.8)	1 (0.3)	4 (0.6)
95% CI[b]	0.2, 2.4	0.0, 1.6	0.2, 1.4
Treatment failure			
n (%)[a]	218 (61.2)	287 (80.8)	505 (71.0)
95% CI[b]	56.0, 66.3	76.4, 84.8	67.5, 74.3
Missing			
n (%)[a]	3 (0.8)	1 (0.3)	4 (0.6)

b Exact 95% CI for percentage calculated by the Clopper-Pearson method

Table 9. Remission Rates for Tertiary Endpoints by Treatment (ITT Population)

	Vosaroxin/Cytarabine N = 356	Placebo/Cytarabine N = 355	Total N = 711
Patients with CR or CRp			
n (%)[a]	124 (34.8)	64 (18.0)	188 (26.4)
95% CI[b]	29.9, 40.0	14.2, 22.4	23.2, 29.8
Difference in percentage	16.8		—
95% CI for difference[c]	10.4, 23.2		—
Chi-square	X^2 = 25.80 p < 0.0001		—
CMH test[d]	X^2 = 27.66 p < 0.0001		—
Patients with CR, CRp, or CRi			
n (%)[a]	132 (37.1)	66 (18.6)	198 (27.8)
95% CI[b]	32.0, 42.3	14.7, 23.0	24.6, 31.3
Difference in percentage	18.5		—
95% CI for difference[c]	12.0, 24.9		—
Chi-square	X^2 = 30.23 p < 0.0001		—
CMH test[d]	X^2 = 32.25 p < 0.0001		—
Patients with CR, CRp, CRi, or PR			
n (%)[a]	135 (37.9)	67 (18.9)	202 (28.4)
95% CI[b]	32.9, 43.2	14.9, 23.3	25.1, 31.9
Difference in percentage	19.0		—
95% CI for difference[c]	12.6, 25.5		—
Chi-square	X^2 = 31.71 p < 0.0001		—
CMH test[d]	X^2 = 33.80 p < 0.0001		—

All p-values are two-sided.

[b] CI, confidence interval; CMH, Cochran-Mantel-Haenszel; CR, complete remission; CRp, complete remission with incomplete platelet recovery; CRi, complete remission with incomplete blood count recovery; PR, partial remission; ITT, intent-to-treat; US, United States

[h] n (%) represents the number and percentage of total patients.

[i] Exact 95% CI for percentage calculated by the Clopper-Pearson method.

[j] 95% CI for the difference in percentage between treatment arms was based on the normal approximation to the binomial distribution.

[k] The CMH test controlling for the randomization strata: disease status (refractory, first relapse with duration of first CR or CRp ≥ 90 days and < 12 months, or first relapse with duration of first CR or CRp ≥ 12 months and ≤ 24 months), age (< 60 years or ≥ 60 years), and geographic location (US or outside US).

EFS

EFS was defined as time from randomization until relapse for responding patients and time until treatment failure for non-responders. EFS was significantly longer in the vosaroxin arm than the placebo (median 1.9 months versus 1.3 months; HR = 0.67, unstratified one-sided p < 0.0001) in all analyses (stratified log-rank one-sided p < 0.0001).

EFS was statistically significantly increased in patients ≥ 60 years with vosaroxin/cytarabine versus placebo/cytarabine (median 2.1 vs 1.3 months, HR = 0.61, one-sided p < 0.0001).

In all three subgroups of disease (ITT population) median EFS was increased in the vosaroxin/cytarabine arm compared with the placebo/cytarabine arm with favorable HRs below one.

The EFS specified per disease state for patients≥ 60 years is summarized in table below. The data showed that also here the EFS was longer in the vosaroxin/cyt group as compared to the placebo/cyt in all three subgroups. Moreover, that the largest effect of the vosaroxin combination was observed in the late relapse patients (more than 2-fold different, while for the other subgroups this was approximately 1.5 fold), though the HR for EFS were rather similar between the subgroups.

Event-Free Survival in Patients ≥ 60 years of Age by Disease Status in the VALOR Study, ITT Population

	Refractory Disease		**Early Relapsed**		**Late Relapsed**	
	Vos/Cyt N = 105	**Pla/Cyt N = 105**	**Vos/Cyt N = 77**	**Pla/Cyt N = 77**	**Vos/Cyt N = 44**	**Pla/Cyt N = 43**
Median EFS duration (95% CI), months	1.7 (1.4, 2.6)	1.2 (1.0, 1.6)	1.7 (1.4, 2.8)	1.3 (1.1, 1.5)	5.5 (2.5, 9.2)	2.3 (1.3, 4.7)
Log rank test wo-sided p-value	p = 0.0005		p = 0.0011		p = 0.0852	
Stratified[a] log-rank test two-sided p-value	p = 0.0005		p = 0.0015		p = 0.0365	
Hazard ratio[b] (95% CI)	0.61 (0.45, 0.81)		0.57 (0.40, 0.81)		0.65 (0.40, 1.07)	
Stratified [a] hazard ratio (95% CI)	0.60 (0.45, 0.81)		0.58 (0.41, 0.82)		0.57 (0.34, 0.79)	

Notes: One month is assumed to be 30.42 days. ITT population includes all patients who were randomized. Early relapsed is defined as first relapse with duration of first CR or CRp ≥ 90 days and < 12 months. Late relapsed is defined as first relapse with duration of first CR or CRp ≥ 12 months and ≤ 24 months.
Abbreviations: CI, confidence interval; CR, complete remission, CRp, complete remission with incomplete platelet recovery, Cyt, cytarabine; EFS, event-free survival; ITT, intent-to-treat; NE, not estimable; Pla, placebo; US, United States; Vos, vosaroxin

[a] Stratification variables used in the model are the randomization strata: geographic location (US or outside US).

[b] Unadjusted Cox Proportional Hazards model was used.

LFS

Leukemia free survival measures duration of response from the start of CR until death or relapse, whichever is earlier (107 patients in the vosaroxin arm, 58 patients in the placebo).

There was a 2.3 month increase in median LFS with the addition of vosaroxin in the subset of patients who had CR, (median of 11.0 months vosaroxin arm versus 8.7 months placebo; HR = 0.89, unstratified one sided p = 0.31).

The results of the sensitivity analysis in which patients with subsequent transplant were censored from the LFS analysis at the time of transplant also favoured the vosaroxin arm (median LFS 7.2 months vs 6.5 months).

In patients ≥ 60 years median duration of LFS in those who achieved CR was prolonged by 3.8 months in the vosaroxin arm compared with the placebo (median of 10.3 months vs 6.5 months, HR = 0.70, one-sided p = 0.10). Median LFS was increased in the vosaroxin/cytarabine arm compared with the placebo/cytarabine arm in all three subgroups by disease subtype, with the largest effect in the early relapse patients (though number of patients with a CR were small). The observed HRs were favorable for patients with refractory and early relapsed disease, with a larger treatment effect in the latter subgroup. In patients with late relapsed disease, the observed HR was above one, favoring the placebo/cytarabine arm.

Leukemia-Free Survival in Patients ≥ 60 years of Age with CR by Disease Status VALOR Study

	Refractory Disease		Early Relapsed		Late Relapsed	
	Vos/Cyt N = 105	Pla/Cyt N = 105	Vos/Cyt N = 77	Pla/Cyt N = 77	Vos/Cyt N = 44	Pla/Cyt N = 43
Patients with a CR	24	9	23	10	25	12
Median LFS duration (95% CI) months	7.2 (4.5, 12.8)	6.5 (0.7, NE)	12.1 (3.0, NE)	5.5 (1.0, 18.0)	10.3 (4.9, 17.2)	8.7 (4.5, NE)
Log-rank test two-sided	p = 0.3975		p = 0.0417		p = 0.7724	
Stratified[a] log-rank test two-sided	p = 0.6952		p = 0.0330		p = 0.7998	
Hazard ratio[b] (95% CI)	0.66 (0.24, 1.76)		0.39 (0.15, 1.00)		1.16 (0.43, 3.10)	
Stratified[a] hazard ratio (95% CI)	0.78 (0.23, 2.65)		0.35 (0.13, 0.96)		1.15 (0.38, 3.47)	

Notes: One month is assumed to be 30.42 days. Includes all patients who were randomized. Early relapsed is defined as first relapse with duration of first CR or CRp ≥ 90 days and < 12 months. Late relapsed is defined as first relapse with duration of first CR or CRp ≥ 12 months and ≤ 24 months.

Abbreviations: CI, confidence interval; CR, complete remission, CRp, complete remission with incomplete platelet recovery, Cyt, cytarabine; LFS, leukemia-free survival; NE, not estimable; Pla, placebo; US, United States; Vos, vosaroxin

[a] Stratification variables used in the model are the randomization strata: geographic location (US or outside US).

[b] Unadjusted Cox Proportional Hazards model was used.

Subsequent treatments/transplant

A total of 210 patients underwent transplant after study treatment with similar rates in both arms: 107 of 356 patients (30.1%) in the vosaroxin arm compared to 103 of 355 patients (29.0%) in the placebo arm.

Despite a significantly higher CR rate in the vosaroxin arm, rates of post-treatment transplantation were similar between arms. This finding may be attributed to the high transplantation rate with or without remission, a change in transplantation practice over the last decade. Among the 210 patients who received transplant, 47.7% (51/107 patients) in the vosaroxin arm and 32.0% (33/103 patients) in the placebo had a CR on study treatment prior to transplantation.

Among patients who achieved prior CR, 47.7% (51/107 patients) in the vosaroxin arm and 56.9% (33/58 patients) in the placebo received transplantation.

The rate of transplantation among those considered eligible at baseline was similar in both treatment arms: 42.8% (98/229) in the vosaroxin arm and 40.3% (94/233) in the placebo.

The rates of subsequent transplantations were similar between arms within all stratification groups and they were highest in patients < 60 years of age and those with late relapse.

Table 10. Subsequent Transplantation by Treatment and Stratification Factors

	Vosaroxin/Cytarabine	**Placebo/Cytarabine**	**Total**
< 60 Years			
n	130	130	260
Transplants performed[a]	60 (46.2%)	59 (45.4%)	119 (45.8%)
≥ 60 Years			
n	226	225	451
Transplants performed[a]	47 (20.8%)	44 (19.6%)	91 (20.2%)
Refractory			
n	152	149	301
Transplants performed[a]	33 (21.7%)	38 (25.5%)	71 (23.6%)
Relapsed with CR1 duration ≥ 90 days and ≤ 12 months			
n	127	129	256
Transplants performed[a]	36 (28.3%)	33 (25.6%)	69 (27.0%)
Relapsed with CR1 duration ≥ 12 months and ≤ 24 months			
n	77	77	154
Transplants performed[a]	38 (49.4%)	32 (41.6%)	70 (45.5%)
Non-US			
n	195	196	391
Transplants performed[a]	51 (26.2%)	49 (25.0%)	100 (25.6%)
US			
n	161	159	320
Transplants performed[a]	56 (34.8%)	54 (34.0%)	110 (34.4%)

Note: Three patients had more than 1 subsequent transplantation reported; the first transplant was summarized for these patients.

Abbreviations: CR1, first complete remission; US, United States

[a]Three patients did not have transplant dates reported but were counted as having had subsequent transplant in the efficacy analysis because transplant conditioning regimens were reported. One patient was excluded because the patient's transplant date was after the analysis data cut off.

Significant improvements in OS were not observed in patient groups with higher transplant rates, despite modest to substantial improvements in CR and EFS,

In the overall ITT population, fewer patients in the vosaroxin arm went on to receive other therapies (including transplantation) after study treatment compared with the placebo (233/356 patients, 65.4% versus 255/355 patients, 71.8%, respectively). Among patients who achieved prior CR, 80.4% (86/107 patients) in the vosaroxin arm and 87.9.9% (51/58 patients) in the placebo received subsequent therapy (including transplant).

In a post-hoc subset analysis, an OS benefit in the overall group of patients ≥ 60 years was observed after long-term follow-up in both transplanted (n = 91; HR = 0.70; 95% CI, 0.43-1.13) and non-transplanted (n = 360; HR = 0.75; 95% CI, 0.60-0.92) patients. Such analyses were not performed for the patients ≥ 60 years per disease state.

Further port hoc analyses Inverse Probability of Censoring Weights (IPCW) provide additional data with favorable HR for vosaroxin. The IPCW analysis showed for unadjusted baseline covariates a HR 0.76, (0.62, 0.94; p 0.011) and when censored for transplant the unstratified HR was 0.81 (0.67, 0.97; p 0.0243) and an stratified HR 0.81 (0.67, 0.98; p 0.0270).

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary of efficacy for study VOS-AML 301 (VALOR)

Title: A Phase 3, Randomized, Controlled, Double-blind, Multinational Clinical Study of the Efficacy and Safety of Vosaroxin and Cytarabine Versus Placebo and Cytarabine in Patients with Relapsed or Refractory Acute Myeloid Leukaemia (VALOR)			
Study identifier	VOS-AML-301		
Design	Phase 3, Randomized, Controlled, Double-blind, Multicentre study		
	Duration of main phase:		17 December 2010 - 26 September 2014
	Duration of Run-in phase:		not applicable
	Duration of Extension phase:		not applicable
Hypothesis	Superiority		
Treatments groups	Vos/Cyt		Vos 90 mg/m^2 days 1, 4 induction 1; 70 mg/m^2 days 1, 4 all other cycles Cyt 1g/m^2 days 1-5 N=356 (352 treated) 1-2 Cy induction + up to 2 Cy consolidation
	Pla/Cyt		Pla days 1, 4 Cyt 1g/m^2 days 1-5 N=355 (353 treated) 1-2 Cy induction + up to 2 Cy consolidation
Endpoints and definitions	Primary endpoint	Overall survival (OS)	time between the date of randomization and the date of death
	Secondary endpoint	Complete remission rate (CR)	percentage of patients whose response is a CR based on modified IWG response criteria, as determined by the CPARR

	Tertiary endpoint	Leukaemia-free survival (LFS)	time between the date of a CR and the date of relapse or death due to any cause, whichever occurs first
	Tertiary endpoint	Event-free survival (EFS)	time between the date of randomization and the date of treatment failure, relapse, or death due to any cause, whichever occurs first
	Tertiary endpoint	CR + CRp rate	% of patients with CR (complete remission) or CRp (CR with incomplete recovery of platelets)
	Tertiary endpoint	Combined CR rate	% of patients with CR or CRp or CRi (CR with incomplete recovery of platelets and neutrophils)
	Tertiary endpoint	Overall remission rate	% of patients with CR or CRp or CRi or PR (Partial remission)
Database lock	26/09/2014		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	**ITT** 26/09/2014		
Descriptive statistics and estimate variability	Treatment group	Vos/Cyt	Pla/Cyt
	Number of subjects	356 (352 treated)	355 (353 treated)
	Median OS (mo)	7.5	6.1
	95% CI	6.4, 8.5	5.2, 7.1
	CR (%)	30.1	16.3
	95% CI	25.3, 35.1	12.6, 20.6
	CR or CRp rate (%)	34.8	18.0
	95% CI	29.9, 40.0	14.2, 22.4
	Combined CR rate (%)	37.1	18.6
	95% CI	32.0, 42.3	14.7, 23.0
	Overall remission rate	37.9	18.9
	95% CI	32.9, 43.2	14.9, 23.3
	Median EFS (mo)	1.9	1.3
	95% CI	(1.6, 2.2)	(1.2, 1.4)
	Median LFS (mo)	11.0	8.7
	95% CI	(8.3, NE)	(6.5, 18.0)

Effect estimate per comparison	OS	Comparison groups	Vos/Cyt vs. Pla/Cyt
		HR	0.87
		95% CI	0.73, 1.02
		P-value (two-sided)	0.0610
	CR	Comparison groups	Vos/Cyt vs. Pla/Cyt
		Difference in %	13.7
		95% CI	7.6, 19.8
		P-value (two-sided)	p < 0.0001
	CR or CRp rate	Comparison groups	Vos/Cyt vs. Pla/Cyt
		Difference in %	16.8
		95% CI	10.4, 23.2
		P-value (two-sided)	< 0.0001
	Combined CR rate	Comparison groups	Vos/Cyt vs. Pla/Cyt
		Difference in %	18.5
		95% CI	12.0, 24.9
		P-value (two-sided)	< 0.0001
	Overall remission rate	Comparison groups	Vos/Cyt vs. Pla/Cyt
		Difference in %	19.0
		95% CI	12.6, 25.5
		P-value (two-sided)	< 0.0001
	Median EFS	Comparison groups	Vos/Cyt vs. Pla/Cyt
		HR	0.67
		95% CI	0.57, 0.78
		P-value (two-sided)	< 0.0002
	Median LFS	Comparison groups	Vos/Cyt vs. Pla/Cyt
		HR	0.89
		95% CI	0.57, 1.40
		P-value (two-sided)	0.62
Analysis population and time point description	**Patients ≥ 60 Years of Age** 26 September 2014		

Descriptive statistics and estimate variability	Treatment group	Vos/Cyt	Pla/Cyt
	Number of subjects	226	225
	Median OS (mo)	7.1	5.0
	95% CI	5.8, 8.1	3.8, 6.4
	CR (%)	31.9	13.8
	95% CI	25.8, 38.4	9.6, 19.0
	CR or CRp (%)	36.3	15.1
	95% CI	30.0, 42.9	10.7, 20.5
	Combined CR rate (%)	38.5	16.0
	95% CI	32.1, 45.2	11.5, 21.5
	Overall remission rate (%)	39.4	16.0
	95% CI	33.0, 46.1	11.5, 21.5
	Median EFS (mo)	2.1	1.3
	95% CI	1.6, 2.8	1.2, 1.6

	Median LFS (mo) 95% CI	10.3	6.5
		6.2, 14.3	4.5, 9.5
Effect estimate per comparison	OS	Comparison groups	Vos/Cyt vs. Pla/Cyt
		HR	0.75
		95% CI	0.62, 0.92
		P-value (two-sided)	0.0030
	CR	Comparison groups	Vos/Cyt vs. Pla/Cyt
		Difference in %	18.1
		95% CI	10.5, 25.6
		P-value (two-sided)	p < 0.0001
	CR or CRp	Comparison groups	Vos/Cyt vs. Pla/Cyt
		Difference in %	21.2
		95% CI	13.3, 29.0
		P-value (two-sided)	< 0.0001
	Combined CR rate	Comparison groups	Vos/Cyt vs. Pla/Cyt
		Difference in %	22.5
		95% CI	14.5, 30.4
		P-value (two-sided)	< 0.0001
	Overall remission rate	Comparison groups	Vos/Cyt vs. Pla/Cyt
		Difference in %	23.4
		95% CI	15.4, 31.4
		P-value (two-sided)	< 0.0001
	Median EFS	Comparison groups	Vos/Cyt vs. Pla/Cyt
		HR	0.61
		95% CI	0.50, 0.75
		P-value (two-sided)	<0.0002
	Median LFS	Comparison groups	Vos/Cyt vs. Pla/Cyt
		HR	0.70
		95% CI	0.40, 1.22
		P-value (two-sided)	0.20

Notes	Stratification factors for this study included disease status (refractory, early first relapse and late first relapse), age (< 60 years or > 60 years – data shown for patients > 60 years), and geographic location (US or outside US – data not shown).

Clinical studies in special populations

No data in patients under 18 years of age have been submitted.

Data on patients with severe liver or renal impairment is missing.

In the clinical development programme baseline liver function in patients 60 years and older exposed to vosaroxin comprised 3 (0.7%) moderate impairment, 58 (13.3%) mild impairment, 366 (83.9%) normal function, and 9 (2.1%) missing information. Alanine transaminase (ALT), Albumin (ALB), Aspartate transaminase (AST), Bilirubin (BIL) and Creatinine clearance (CRCL) were investigated in a population PK model and none of the parameters were identified as a significant covariate. Results of

VOS-ADME-101 and the population PK analyses suggest that vosaroxin exposure would not be significantly affected in patients with hepatic impairment. However, there is limited experience in patients with pre-existing mild to moderate hepatic impairment and no experience in patients with pre-existing severe hepatic impairment. The safety and efficacy of vosaroxin have not been established in patients with impaired hepatic function.

At baseline the majority of patients exposed to vosaroxin had normal renal function: 4 (0.9%) moderate impairment, 42 (9.6%) mild impairment, 382 (87.6%) normal function, and 8 (1.8%) missing information.

Data in elderly have been submitted. In the VALOR study the mean age was 60.6 years (SD 12.01) and the median age was 63 years (min 18 and max. 82). Age is not a significant covariate of the PK of vosaroxin.

Overall survival (OS) is summarized by age category in Table 3. There was no pattern to suggest a different treatment effect across the age categories and the results are consistent with those for the VALOR ≥ 60 years of age population.

Table 3. Overall Survival Results in VALOR Patents ≥ 60 Years of Age by Age Category, ITT Population

	Age 60-64 years		Age 65-74 years		Age 75-84 years		Age ≥ 60 years	
	Vos/Cyt (N = 56)	Pla/Cyt (N = 68)	Vos/Cyt (N = 153)	Pla/Cyt (N = 140)	Vos/Cyt (N = 17)	Pla/Cyt (N = 17)	Vos/Cyt N = 226	Pla/Cyt N = 225
Median duration of OS (95% CI) (months)	8.1 (4.6, 9.8)	5.2 (3.4, 7.6)	7.0 (5.3, 8.1)	5.0 (3.8, 7.5)	5.5 (1.3, 12.4)	3.3 (1.1, 7.1)	7.1 (5.8, 8.1)	5.0 (3.8, 6.4)
Log-rank test two-sided p-value	p = 0.0592		p = 0.0765		p = 0.2437		p = 0.0030[a]	
Stratified[c] log-rank test two-sided p-value	p = 0.2106		p = 0.0238		p = 0.2897		p = 0.0018[a]	
Hazard ratio[b] (95% CI)	0.69 (0.46, 1.02)		0.80 (0.62, 1.03)		0.66 (0.32, 1.34)		0.75 (0.62, 0.92)	
Stratified[c] Hazard ratio (95% CI)	0.76 (0.50, 1.17)		0.74 (0.57, 0.96)		0.63 (0.27, 1.48)		0.74 (0.60, 0.91)	

Note: The ITT population consisted of all patients randomized. n (%) represents the number and percentage of ITT patients.

Abbreviations: CI, confidence interval; CR, complete remission; CRp, complete remission with incomplete platelet recovery; CI, confidence interval; CR, Complete remission; Cyt, cytarabine; ITT, intent-to-treat; Pla, placebo; Vos, vosaroxin

a Test statistics are adjusted using the methodology of Cui 1999 to account for the pre-specified sample size adjustment at the interim.

b Unadjusted Cox Proportional Hazards Model is used

c Stratification variables used in the model are the randomization strata: disease status (refractory, first relapse with duration of first CR or CRp ≥ 90 days and < 12 months, or first relapse with duration of first CR or CRp ≥ 12 months and ≤ 24 months), and geographic location (US or outside US).

Supportive study - Study SPO-014

This was a Phase 2, open-label, multicentre study of single agent vosaroxin administered in 3 treatment schedules in patients ≥ 60 years old with untreated AML (de novo or secondary). Eligible patients had to present with at least 1 of the following adverse prognostic factors: age ≥ 70 years, secondary AML, ECOG performance status of 2 or intermediate or unfavourable karyotype. Patients with acute promyelocytic leukaemia were excluded.

The study was conducted at 17 sites in US (2008-2009).

The primary objective was to evaluate the combined CR rate (CR + CRp) of vosaroxin. Secondary objectives included LFS and OS.

A total of 113 patients were enrolled and treated (All Treated population) with vosaroxin IV according to one of the following schedules for up to 4 treatment cycles (1 or 2 induction and up to 2 consolidation):

- Schedule A, weekly × 3 (Days 1, 8, and 15) at 72 mg/m^2 (n=29)
- Schedule B, weekly × 2 (Days 1 and 8) at 72 mg/m^2 (n=35)
- Schedule C 72, twice weekly × 1 (Days 1 and 4) at 72 mg/m^2 (n=29)
- Schedule C 90, twice weekly × 1 (Days 1 and 4) at 90 mg/m^2 (n=20)

The majority of patients were male (64.6%) with mean age of 73.6 years (range 60-89) and of white race (90%).

Remissions were observed for all treatment schedules and across all risk factors.

In the All Treated population (N = 113), a total of 36 (31.9%) patients achieved CR/CRp (33 with CR and 3 with CRp). The percentage of patients achieving remission was similar between Schedule B and Schedule C 90 (25.7% and 25.0%, respectively), higher in the Schedule C 72 (34.5%) and highest in Schedule A (41.4%).

In patients who achieved CR or CRp, the median duration of LFS was 6.1 months (range, 1.3 to 23.8 months). The median OS was 7.0 months (range, 0.2 to 33.0 months).

Some patients completed up to 4 cycles but the majority had only one cycle (57.5%). No clinically differences were seen across groups for TEAEs but incidence of SAEs was lowest in Schedule C 72.

Vosaroxin demonstrated single-agent activity in patients ≥60 years with newly-diagnosed AML and at least one poor-prognostic factor.

3.3.6. Discussion on clinical efficacy

Design and conduct of clinical studies

Efficacy of vosaroxin in combination with cytarabine is based on a single phase 3 study (VALOR).The study is considered of adequate design and with appropriate clinical endpoints for the indication in AML (primary endpoint OS). From a clinical point of view the percentage of patients who have had post-treatment (subsequent) transplantation (tertiary endpoint) is of interest, as it provides information on the use of vosaroxin/cytarabine combination as a bridging strategy to allogeneic haematopoietic stem cell transplantation.

The patient inclusion/exclusion criteria reflect the heterogeneous population of AML adult patients (only AML M3 and those with CNS involvement were excluded) in first relapse or refractory that is in a good to reasonable condition.

The selection of doses/schedules has been justified.

The choice of the intermediate dose of cytarabine as comparator was supported by SAWP (SA May 2010) as the optimal regimen for the treatment of relapsed/refractory AML was deemed unclear. No direct comparative data on OS with more (also commonly used) intensive regimens in which intermediate dose cytarabine is used in combination with other cytotoxic drugs (e.g. the FLAG-IDA or MEC regimen, are available.

Few more patients in vosaroxin arm of VALOR received induction and consolidation treatment than in the control, but the majority (55% vosaroxin arm vs 69% placebo arm) received 1 induction cycle.

As the true effect of the experimental treatment versus control was not known an adaptive design was employed. The design is appropriate and well executed and followed previous CHMP scientific advice. However, the boundary for statistical significance for the primary endpoint was set at a p value of 0.0494 (two sided). This corresponds to an type I error of the design (interim and final analysis) of 0.05, but which is not considered sufficiently extreme as described on CHMP guideline for marketing authorisation applications based on single pivotal study(*Points to consider on application with 1. Meta-analyses 2. One pivotal study - CPMP/EWP/2330/99*).

Efficacy data and additional analyses

The study failed its primary analysis with a result (un-stratified median OS in ITT population 7.5 months active versus 6.1 months control; HR 0.87, p 0.0610) below the hurdle of the pre-specified statistical significance. The stratified analysis reaches the pre-specified statistical significance (median OS 7.5 m vs 6.1 m, HR 0.83, p 0.024). However, the statistical significant difference with stratified analysis is not considered compelling for a single pivotal study.

In a pre-planned analysis of 451 patients of ≥ 60 years that represent around two thirds of the study population, a greater OS benefit was observed compared to the full ITT population (median OS 7.1 months vs 5.0 months; HR 0.75, p = 0.0030. The benefit of vosaroxin in the ITT population is driven by the results in patients above 60 years. The Applicant has proposed the indication for the subgroup of patients ≥ 60 years although this subgroup analysis was not pre-specified for confirmatory testing. As an explanation for the lack of effect in patients younger than 60 years (HR 1.08), the Applicant argued that younger apparently had a more cytarabine-sensitive leukaemia, which may have affected OS in a positive way in both arms. This notion fits with the observation that the placebo arm had better OS results than expected (i.e. 6.1 months while 5.0 months was expected). However, replication of the subgroup findings for ≥ 60 year by age on OS from other relevant trials is missing.

A plausible explanation why vosaroxin exhibits a different efficacy in the age subgroup is predominantly based on its cytotoxic activity shown in *in vitro* models with p53 mutations and those with overexpression of the drug efflux transporter P-glycoprotein 1. These mechanisms of drug resistance may occur more often in older patients based on literature data. No data on p53 mutations were, however, available within the VALOR study.

Data on other subgroup analysis within the patient group of 60 years and older reveal that patients with late relapse do not benefit from adding vosaroxin to cytarabineand that efficacy in terms of OS appears to be observed in patients ≥ 60 years with refractory or early first relapse.

The results in endpoints CR and EFS reached a statistically significant difference in favour of the combination for all disease status groups, but this did not translate in an OS benefit for the late relapse group. For LFS, median duration numerically favoured the vosaroxin arm among the disease status groups with the largest absolute difference seen in the early relapse group. However, interpretation of the LFS data is hampered by the low number of patients with CR and therefore no firm conclusions can be drawn on LFS. Significant improvements in OS were not observed in patient groups with higher transplant rates (patients < 60 years and patients with late relapse. It was also observed there was no difference between arms in the percentage of patients transplanted following treatment, for overall ITT population as well as across strata, although the number of patients in CR who underwent a transplant was higher in the experimental arm than in the control arm.

In a post-hoc subset analysis, an OS benefit in the overall group of patients ≥ 60 years was observed after long-term follow-up in both transplanted (n = 91; HR = 0.70; 95% CI, 0.43-1.13) and non-transplanted (n = 360; HR = 0.75; 95% CI, 0.60-0.92) patients. However, transplantation is a post-baseline covariate and the choice to transplant a patient is a result of several variables, including cytogenetic risk at baseline and the result of therapy. As such these are non-randomised comparisons

and should be interpreted with caution. Moreover, this analysis does not address the observation of the lack of effect in the late relapse patients, as no results were provided showing that the effect of transplantation also holds for patients ≥60 years with late relapse, while it is clear that the benefit in the ≥60 years group is driven by the refractory/early relapse patients (n=364, HR=0.69, 95% CI = 0.55-0.86 in contrast to the late relapse group n=87, HR=1.06; 95% CI=0.65-1.72). Moreover, confounding as an explanation was not convincingly investigated (no post-hoc comparison of OS with/out transplant in the subgroup ≥ 60 with late relapse; no modeling that age over 60 could modify the influence of baseline and time-varying variables in the presented IPCW analyses for differential effect for disease x age subgroups, while the biology of disease is considered different for age over 60). In addition, an impact on OS of the increased risk of lethal infections within the patients with late relapse while on vosaroxin can not be ruled out (see safety section).

Cytogenetics is recognized as a key prognostic factor. No significant imbalance between arms was noted at baselineand a little more than half of the patients in each arm had intermediate cytogenetic risk. Only a few patients had a favorable profile (less than 10 subjects per arm) and the rest of the patients had an unfavorable cytogenetic profile. An improvement in OS was observed for vosaroxin/cy compared with placebo/cy in both the intermediate and unfavorable risk groups for both the ITT and the ≥ 60 years populations. The favorable group was too small to draw a conclusion on the data. In the ≥ 60 years population, the greatest improvement was found in the unfavorable risk group with a HR 0.49 [0.31, 0.80]. Cytogenetic karyotype is reported to be the single most important factor after age in AML for predicting outcome. The treatment benefit with vosaroxin versus placebo in patients with unfavourable cytogenetics is clinically relevant as these patients carry a very poor prognosis. This outcome is in line with the notion that vosaroxin exhibits activity in those who have drug resistance/refractoriness leukaemia commonly associated to unfavourable cytogenetics.

Molecular characteristics were available for only approximately one-fifth of the patients and wild-type molecular characteristics were more common than mutated for both NPM1 and FLT3. Besides that the number of patients involved is too low to draw a firm conclusion, it was not clear from the information if there were patients with complex or NPM-1/FLT3-ITD combined abnormalities that may alter the prognosis in comparison to that of patients with leukaemia that harbours the single abnormality.

OS data was mature at primary analysis but updated data as of 22 January 2016 with 83 patients alive (46/356 (12.9%) in the vosaroxin arm and 37/355 (10.4%) in the placebo arm)has shown results for ITT population with HR 0.88 (0.75, 1.03) and those above 60 years age with HR 0.75 (0.62, 0.91) consistent with primary analysis. The benefit with vosaroxin in older subgroup is maintained with long term follow up.

Safety and efficacy of the product have not been established in children aged less than 18 years

3.3.7. Conclusions on clinical efficacy

Efficacy is based on a single pivotal trial that failed its primary objective. The Applicant is seeking approval in an indication restricted to the subgroup of patients aged over 60 years of age.

Overall, the primary OS results in the ITT showed only a trend towards a positive result for the vosaroxin arm (p>0.05), and upon further analysis the results appeared to be driven by the subgroup of patients ≥60 years. No strong internal or external replication of these study results have been provided.

The patient population ≥60 years can be considered a distinct entity based on baseline and disease characteristics. As the median age of AML diagnosis is around 68 years, this subgroup does represent the majority of AML patients. There was no consistency in the results among the patients in the age-

defined subgroup ≥60 years when subdividing the patients per disease state, i.e. there appears to be efficacy in the early relapse and the refractory patients, while no effect on OS was seen in the subgroup with late relapse. This may be partly explained by the high transplantation rate, but this explanation is presently not supported by a convincing analyses or data. In addition, an effect of the increased infection rate in this distinct patient group on OS can not be excluded (see also safety section).

So approval in a subgroup(s) of patients without a study replicating the results or a clear explanation for inconsistent results among subgroup(s) of patients is also a major concern, in particular in the context of a (negative) single pivotal trial.

The applicant is therefore requested to provide (external) replication of the age-driven subgroup data and discussion on the inconsistency of the disease state subgroup results. The latter should include further justification that adequate prophylaxis could improve the safety outcome and discuss the impact on OS for patients ≥60 years with late relapse (MOs).

3.3.8. Clinical safety

Patient exposure

Safety data have been collected in 1126 patients who have been treated with vosaroxin, including 4 haematogical malignancy studies (VALOR, SPO-04, SPO-012, SPO-014; n=648), 6 solid tumours studies (n=284) with lower exposure to vosaroxin compared to haematology studies, a mass balance study (n=6), and 4 investigator sponsor trials and one investigator sponsored single patient compassionate use (n=188).

For the purpose of this application discussion is focused on data from the VALOR study with additional references to haematology malignancy studies, pooled summary all vosaroxin-treated patients in haematology malignancy studies (including post hoc analysis for patients ≥ 60 years).

All analyses were performed on the safety population (all patients who received any amount of study drug, vosaroxin, cytarabine or placebo).

Of these patients, 447 were aged ≥ 60 years: 262 in the vosaroxin/cytarabine arm and 221 in the placebo/cytarabine arm. For the patients aged ≥ 60 years, the mean age was 68.0 years in the vosaroxin/cytarabine arm, and 67.8 years for the placebo/cytarabine group (overall population: 61.1 years vs. 60.1 years). The majority of the patients were white (70.7% vos/cyt vs 68.3% plac/cyt), and male (56.9% vos/cyt vs 53.7% plac/cyt). With the exception of age, demographic characteristics for the patients ≥ 60 years were similar to those of the total population. Medical history, prior medication and co-morbidities were comparable across the vosaroxin/cytarabine arm and the placebo/cytarabine arm.

Usage of concomitant medications was high with no notable differences between the two arms in the VALOR study except for the use of anti-diarrhoeal, intestinal anti-inflammatory/anti-infective agents (44.8% vosaroxin vs 20.9% placebo) and for immunostimulants (40.8% vosaroxin vs 22% placebo).

Patient disposition for the hematologic malignancy studies in table below showed 11.1% of patients who received vosaroxin completed all treatment and the majority of patients discontinued because of disease progression (54.2%). In the VALOR study, more patients in the placebo arm discontinued treatment because of disease progression (73.1% vs 50.1%).

Table 11 Patient Disposition (Safety Population – All Patients, Hematologic Malignancy Studies)

	SPO-0004 (N=73) n (%)	SPO-0012 (N=108) n (%)	SPO-0014 (N=113) n (%)	VALOR		Total Vosaroxin (N=648) n (%)
				Vos/Cyt (N=355) n (%)	Pla/Cyt (N=350) n (%)	
Primary reason for treatment discontinuation						
Completed treatment[a]	2 (2.7)	12 (11.1)	18 (15.9)	40 (11.3)	18 (5.1)	72 (11.1)
Adverse event	1 (1.4)	3 (2.8)	7 (6.2)	9 (2.5)	8 (2.3)	20 (3.1)
Death	8 (11.0)	1 (0.9)	20 (17.7)	32 (9.0)	10 (2.9)	61 (9.4)
Treatment failure/disease relapse or progression	46 (63.0)	71 (65.7)	56 (49.6)	178 (50.1)	256 (73.1)	351 (54.2)
Physician decisions	8 (11.0)	3 (2.8)	5 (4.4)	47 (13.2)	24 (6.9)	63 (9.7)
Withdrawal by patient	2 (2.7)	0	0	1 (0.3)	4 (1.1)	3 (0.5)
Other	6 (8.2)	18 (16.7)	7 (6.2)	48 (13.5)	30 (8.6)	78 (12.0)
Primary reason for study discontinuation						
Completed study[b]	–	1 (0.9)	–	76 (21.4)	58 (16.6)	77 (16.6)
Adverse event	–	1 (0.9)	–	0	0	1 (0.2)
Death	–	92 (85.2)	–	273 (76.9)	288 (82.3)	365 (78.8)
Lost to follow-up	–	14 (13.0)	–	3 (0.8)	3 (0.9)	17 (3.7)
Withdrawal by patient	–	0	–	2 (0.6)	1 (0.3)	2 (0.4)
Other	–	0	–	1 (0.3)	0	1 (0.2)

Source: ISS Table 1

Total Vosaroxin column includes all patients from SPO-0004, SPO-0012, SPO-0014 and Vos/Cyt patients from VALOR. The patient enrolled in two studies is counted only once (see Section 2.7.4.1.1.2.4.1).
Safety population includes all patients who receive any amount of study drug (vosaroxin, placebo, or cytarabine).
In VALOR, the assignment of patients to treatment group is based on the treatment actually received.
Denominator for total vosaroxin study discontinuation is based on VALOR and SPO-0012 and is 463.
Abbreviations: Cyt, cytarabine; Pla, placebo; Vos, vosaroxin

[a] Completed treatment for VALOR is the number of patients who completed the "maximum allowed treatment."
[b] Completed study for VALOR is the number of patients ongoing at database lock.

The median time of the last study treatment for patients (safety population) who discontinued treatment due to physician decision was shorter in the vosaroxin/cy arm (21.0 days) than in the placebo/cy (42.0 days). A higher number of patients in the vosaroxin arm (40 /85.1% of those discontinued) received one induction cycle compared to the placebo (14 /58.3% of those discontinued). The majority of patients in both arms who discontinued treatment due to physician decision achieved a response of CR, CRp, or CRi (40 of 47 [85.1%] and 20 of 24 [83.3%] with vosaroxin/cytarabine and placebo/cytarabine, respectively). More of these patients treated with vosaroxin (n=25) underwent subsequent transplantation compared to placebo (n=14).

Mean exposure (duration between the first and last dose of study treatment) for the 648 patients who received vosaroxin was 31.2 (SD 46.3) days (range 1 to 537 days) and it varied across studies: in VALOR, it was reported as 37.9 (53.0) days. The majority patients received induction 1 only. In the VALOR study, the majority of patients received induction 1 only in both arms but the percentage was higher for the placebo than vosaroxin arm (68.9% vs 55.2%). More patients in the vosaroxin arm received induction 1 and consolidation 1 or consolidation 1 and 2 than in the placebo (13.2% versus 4.9% and 11.8% versus 4.0% respectively).

The median cumulative exposure in VALOR was 181.4 mg/m^2 for vosaroxin and 5 g/m^2 for cytarabine in both arms.

Table 12 Extent of Exposure to Study Treatment (Safety Population – All Patients, Hematologic Malignancy Studies)

	SPO-0004 (N=73)	SPO-0012 (N=108)	SPO-0014 (N=113)	VALOR		Total Vosaroxin (N=648)
				Vos/Cyt (N=355)	Pla/Cyt (N=350)	
Duration of exposure (days)[b]						
Mean (SD)	43.3 (83.30)	18.6 (30.48)	37.9 (52.95)	30.3 (34.65)	20.7 (28.46)	31.2 (46.34)
Median	15	6	15	6	5	8
Min, Max	1, 537	5, 184	1, 391	2, 173	4, 126	1, 537
Patients who received study treatment for, n (%):[c]						
Induction only	–	86 (79.6)	65 (57.5)	196 (55.2)	241 (68.9)	347 (60.3)[a]
Induction 1 and 2	–	7 (6.5)	18 (15.9)	62 (17.5)	59 (16.9)	87 (15.1)[a]
Induction 1 and 2, and consolidation 1	–	0	2 (1.8)	5 (1.4)	11 (3.1)	6 (1.0)[a]
Induction 1 and 2, and consolidation 1 and 2	–	0	6 (5.3)	3 (0.8)	8 (2.3)	9 (1.6)[a]
Induction 1 and consolidation 1	–	11 (10.2)	10 (8.8)	47 (13.2)	17 (4.9)	68 (11.8)[a]
Induction 1 and consolidation 1 and 2	–	4 (3.7)	12 (10.6)	42 (11.8)	14 (4.0)	57 (9.9)[a]
> 4 cycles[d]	–	0	0	0	0	1 (0.2)[a]
Other	–	0	0	0	0	0
Number of cycles of treatment received						
n	73	–	–	–	–	73
Mean (SD)	1.5 (0.91)	–	–	–	–	1.5 (0.91)
Median	1	–	–	–	–	1
Min, Max	1, 5	–	–	–	–	1, 5

Source: ISS Table 9

Total Vosaroxin column includes all patients from SPO-0004, SPO-0012, SPO-0014 and Vos/Cyt patients from VALOR. The patient enrolled in two studies is counted only once (see Section 2.7.4.1.1.2.4.1).
Safety population includes all patients who receive any amount of study drug (vosaroxin, placebo, or cytarabine).
In VALOR, the assignment of patients to treatment group is based on the treatment actually received.
Abbreviations: Cyt, cytarabine; Max, maximum; Min, minimum; Pla, placebo; SD, standard deviation; Vos, vosaroxin

[a] The denominator for each category of 'Number of Patients who Received Study Treatment' for the total vosaroxin group excludes SPO-0004 and is N=575. Data for SPO-0004 was only recorded as total number of cycles rather than as induction and consolidation cycles.

[b] Duration of exposure to study treatment was calculated as the date of last dose of study drug minus the date of first study drug +1.

[c] Induction cycles include induction AND reinduction cycles in applicable studies. Each patient is counted once only.

[d] Greater than 4 cycles includes the subject who was enrolled in two studies.

There were very few dosing delays or dose adjustments in the VALOR study.

Only one patient was reported with AE that led to a dose reduction, 12 subjects had dose adjustments to either vosaroxin or placebo , 7 (2.0%) in the vosaroxin and 5 (1.4%) in the placebo. There were no important differences between the two groups in the number or size of the dose adjustments.

There were 7 subjects, all in the vosaroxin group, who had dose adjustments to their cytarabine dose. However, the number of patients with increased doses (3 patients) and decreased doses (4 patients) of cytarabine was similar.

Similar and low numbers of patients in each arm had any dose delay: 9 (2.5%) patients in the vosaroxin group and 8 (2.3%) in the placebo. For all these patients, except two, the dosing delay was between 1 and 3 days.

Few patients missed doses of study medication (either vosaroxin/placebo or cytarabine): 7 (2.0%) patients in the vosaroxin group and 4 (1.1%) in the placebo group. No patient missed more than 1 dose of vosaroxin or placebo.

Overall the pattern of dose delays and adjustments was very similar in the two treatment groups.

Patients 60 years and older

There were 436 patients in hematologic malignancy studies treated with vosaroxin who were ≥60 years and the exposure was generally similar to those seen for all patients treated in the overall safety population in the hematologic malignancy studies. In VALOR, more patients ≥ 60 years in the placebo arm (vs vosaroxin) discontinued treatment because of disease progression (72.9% vs 46.0%) whilst more patients in the vosaroxin arm completed the study (18.6% vs 9.5% placebo). The primary reason for study discontinuation was death.

Table 13 Patient disposition in VALOR study for all patients and for those ≥60 years

	VALOR All Patients		VALOR Patients ≥ 60 Years of Age	
	Vos/Cyt N = 355	Pla/Cyt N = 350	Vos/Cyt N = 226	Pla/Cyt N = 221
Treatment Disposition				
Completed treatment[a]	40 (11.3)	18 (5.1)	34 (15.0)	11 (5.0)
Primary reason for treatment discontinuation:				
Adverse event	9 (2.5)	8 (2.3)	5 (2.2)	6 (2.7)
Death	32 (9.0)	10 (2.9)	24 (10.6)	7 (3.2)
Treatment failure/disease relapse or progression	178 (50.1)	256 (73.1)	104 (46.0)	161 (72.9)
Physician decisions	47 (13.2)	24 (6.9)	32 (14.2)	16 (7.2)
Other/Withdrawal by patient	49 (13.8)	34 (9.7)	27 (11.9)	20 (9.0)
Study Disposition				
Completed study[b]	76 (21.4)	58 (16.6)	42 (18.6)	21 (9.5)
Discontinued Due to Death	273 (76.9)	288 (82.3)	182 (80.5)	198 (89.6)

Source: Table 2.7.4-4 and Table 2.7.4-7

Note: Safety population included all patients who received any amount of study drug (vosaroxin, placebo, or cytarabine). The assignment of patients to treatment group was based on the treatment actually received.

Abbreviations: Cyt, cytarabine; Pla, placebo; Vos, vosaroxin

[a] Completed treatment for VALOR is the number of patients who completed the "maximum allowed treatment."

[b] Completed study for VALOR is the number of patients ongoing at database lock.

The extent of exposure to study medication for patients ≥ 60 years of age was also similar to the overall safety population. In the VALOR study, the majority received one induction cycle only, especially in placebo arm (54% vosaroxin vs 70.1% placebo) whilst more patients in the vosaroxin arm than placebo received induction 1 and consolidation 1 (12.8% vs 3.6%) or consolidation 1 and 2 (15.9% vs 3.2%).

Cumulative exposure to study treatment was also similar to the overall safety population. In VALOR the median cumulative exposure for vosaroxin was 395 mg (185.7 mg/m^2), and for cytarabine (5 g/m^2) in both arms.

Adverse events

A total of 99.8% of patients who received vosaroxin reported a TEAE and a TEAE ≥ Grade 3 was reported for 93.5%. The incidence of TEAEs, TEAEs ≥ Grade 3, and treatment-related TEAEs in vosaroxin-treated patients was generally similar across the studies and were similar to those seen in patients ≥ 60 years.

In VALOR, 99.7% of patients in each arm reported TEAEs with higher percentages of patients treated vosaroxin arm vs placebo for whom TEAEs ≥ Grade 3 (94.1% vs 84.3%), SAEs (55.5% vs 35.7%), SAEs ≥ Grade 3 (53.5% vs 32.9%), treatment related SAEs (32.7% vs 16.6%), and TEAEs/SAEs leading to death (14.1% vs 7.4%) were reported. A summary of overall TEAEs occurring in the hematologic malignancy studies is presented in below.

Table 14 Overall summary of Treatment-emergent Adverse Events (Safety population-All patients Haematology Malignancy Studies)

Patients Reporting at Least One:	SPO-0004[a] (N=73) n (%)	SPO-0012 (N=108) n (%)	SPO-0014 (N=113) n (%)	VALOR		Total Vosaroxin[b] (N=648) n (%)
				Vos/Cyt (N=355) n (%)	Pla/Cyt (N=350) n (%)	
TEAE	73 (100)	108 (100)	113 (100)	354 (99.7)	349 (99.7)	647 (99.8)
Grade ≥ 3 TEAE[c]	63 (86.3)	100 (92.6)	110 (97.3)	334 (94.1)	295 (84.3)	606 (93.5)
SAE	19 (26.0)	50 (46.3)	92 (81.4)	197 (55.5)	125 (35.7)	357 (55.1)
Grade ≥ 3 SAE[c]	19 (26.0)	48 (44.0)	90 (79.6)	190 (53.5)	115 (32.9)	346 (53.4)
TEAE leading to study treatment discontinuation	5 (6.8)	7 (6.5)	20 (17.7)	6 (1.7)	8 (2.3)	38 (5.9)
TEAE leading to death[d]	6 (8.2)	9 (8.3)	26 (23.0)	50 (14.1)	26 (7.4)	91 (14.0)
SAE leading to death[d]	6 (8.2)	9 (8.3)	25 (22.1)	50 (14.1)	26 (7.4)	90 (13.9)
TEAE related to Vos or Pla[e]	71 (97.3)	106 (98.1)	112 (99.1)	322 (90.7)	290 (82.9)	610 (94.1)
TEAE related to Cyt[e]	NA	105 (97.2)	NA	331 (93.2)	305 (87.1)	436 (94.2)
TEAE related to either Vos or Pla, or Cyt[e]	71 (97.3)	106 (98.1)	112 (99.1)	331 (93.2)	305 (87.1)	619 (95.5)
Grade ≥ 3 related to Vos or Pla[c, e]	55 (75.3)	89 (82.4)	90 (79.6)	258 (72.7)	193 (55.1)	491 (75.8)
Grade ≥ 3 related to Cyt[c, e]	NA	88 (81.5)	NA	266 (74.9)	204 (58.3)	354 (76.5)
Grade ≥ 3 related to either Vos or Pla or Cyt[c,e]	55 (75.3)	89 (82.4)	90 (79.6)	267 (75.2)	204 (58.3)	500 (77.2)
SAE related to Vos or Pla[e]	12 (16.4)	30 (27.8)	55 (48.7)	113 (31.8)	56 (16.0)	209 (32.3)
SAE related to Cyt[e]	NA	31 (28.7)	NA	111 (31.3)	58 (16.6)	142 (30.7)
SAE related to either Vos or Pla, or Cyt[e]	12 (16.4)	31 (28.7)	55 (48.7)	116 (32.7)	58 (16.6)	213 (32.9)

Source: ISS Table 11

Total Vosaroxin column includes all patients from SPO-0004, SPO-0012, SPO-0014 and Vos/Cyt patients from VALOR. The patient enrolled in two studies is counted only once (see Section 2.7.4.1.1.2.4.1).

Safety population included all patients who received any amount of study drug (vosaroxin, placebo, or cytarabine). In VALOR, the assignment of patients to treatment group was based on the treatment actually received.

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; Cyt, cytarabine; NA, not applicable; Pla, placebo; SAE, serious adverse event; TEAE = treatment-emergent adverse event; Vos, vosaroxin;

[a] Includes leukemia-associated symptoms, which were considered to be related and not serious.

[b] Cytarabine was not given in SPO-0004 and SPO-0014. The Total Vosaroxin denominator for related to cytarabine rows exclude SPO-0004 and SPO-0014; N=463.

[c] Patients reporting more than one AE were counted only once using the highest CTCAE toxicity grade. VALOR used CTCAE v4.03. All other studies used CTCAE v3.0.

[d] Only TEAEs where the event contributed to death are considered. This includes all "fatal" events reported in VALOR, but only "fatal" events with an additional entry of "contributed to death" for SPO-0004, SPO-0012, and SPO-0014.

[e] An event was considered related if there were any reasonable possibility the event was cause by the drug or drugs of interest, as assessed by the Investigator. Events with missing relationship were considered related.

Common AE

The most commonly reported TEAEs in vosaroxin treated patients were diarrhoea (68.7%), nausea (63.9%), febrile neutropenia (52.9%), stomatitis (51.1%), hypokalaemia (51.1%), and decreased appetite (46.0%).

In VALOR, the TEAEs reported for a higher percentage of patients in vosaroxin arm versus placebo were febrile neutropenia (47.9% vs 34.3%), diarrhoea (68.7% vs 34.6%), nausea (61.4% vs 47.7%), stomatitis (49.0% vs 18.9%), vomiting (38.0% vs 20.9%), hypokalaemia (47.9% vs 29.1%), decreased appetite (35.5% vs 16.9%), hypomagnesaemia (26.8% vs 16.6%), and abdominal pain (22.3% versus 13.1%).

The results in patients ≥ 60 years (all studies and VALOR both arms) were very similar to those observed for all patients in the hematologic malignancy studies.

Table 15 Treatment-emergent Adverse Events Occurring in at Least 20% of Patients in the Total Vosaroxin Group (Safety Population – All Patients, Hematologic Malignancy Studies)

System Organ Class Preferred Term	SPO-0004[a] (N=73) n (%)	SPO-0012 (N=108) n (%)	SPO-0014 (N=113) n (%)	VALOR		Total Vosaroxin (N=648) n (%)
				Vos/Cyt (N=355) n (%)	Pla/Cyt (N=350) n (%)	
Patients with any TEAE	73 (100)	108 (100)	113 (100)	354 (99.7)	349 (99.7)	647 (99.8)
Blood and lymphatic system disorders	**60 (82.2%)**	**94 (87.0%)**	**107 (94.7%)**	**245 (69.0%)**	**227 (64.9%)**	**505 (77.9%)**
Febrile neutropenia	42 (57.5)	67 (62.0)	65 (57.5)	170 (47.9)	120 (34.3)	343 (52.9)
Anaemia	24 (32.9)	55 (50.9)	62 (54.9)	95 (26.8)	105 (30.0)	235 (36.3)
Thrombocytopenia	25 (34.2)	50 (46.3)	69 (61.1)	89 (25.1)	91 (26.0)	232 (35.8)
Neutropenia	20 (27.4)	24 (22.2)	35 (31.0)	70 (19.7)	51 (14.6)	148 (22.8)
Gastrointestinal disorders	**69 (94.5%)**	**108 (100.0%)**	**112 (99.1%)**	**337 (94.9%)**	**307 (87.7%)**	**625 (96.5%)**
Diarrhoea	36 (49.3)	81 (75.0)	85 (75.2)	244 (68.7)	121 (34.6)	445 (68.7)
Nausea	46 (63.0)	72 (66.7)	79 (69.9)	218 (61.4)	167 (47.7)	414 (63.9)
Stomatitis	20 (27.4)	68 (63.0)	69 (61.1)	174 (49.0)	66 (18.9)	331 (51.1)
Vomiting	24 (32.9)	53 (49.1)	47 (41.6)	135 (38.0)	73 (20.9)	258 (39.8)
Constipation	20 (27.4)	44 (40.7)	34 (30.1)	136 (38.3)	141 (40.3)	234 (36.1)
Abdominal pain	16 (21.9)	32 (29.6)	24 (21.2)	79 (22.3)	46 (13.1)	151 (23.3)
General disorders and administration site conditions	**57 (78.1%)**	**95 (88.0%)**	**103 (91.2%)**	**285 (80.3%)**	**265 (75.7%)**	**539 (83.2%)**
Fatigue	33 (45.2)	43 (39.8)	54 (47.8)	107 (30.1)	94 (26.9)	236 (36.4)
Oedema peripheral	23 (31.5)	39 (36.1)	58 (51.3)	96 (27.0)	69 (19.7)	215 (33.2)
Pyrexia	20 (27.4)	26 (24.1)	28 (24.8)	119 (33.5)	107 (30.6)	193 (29.8)
Chills	19 (26.0)	47 (43.5)	34 (30.1)	61 (17.2)	46 (13.1)	160 (24.7)
Asthenia	17 (23.3)	30 (27.8)	33 (29.2)	60 (16.9)	43 (12.3)	139 (21.5)
Metabolism and nutrition disorders	**53 (72.6%)**	**105 (97.2%)**	**105 (92.9%)**	**270 (76.1%)**	**212 (60.6%)**	**532 (82.1%)**
Hypokalaemia	11 (15.1)	79 (73.1)	71 (62.8)	170 (47.9)	102 (29.1)	331 (51.1)
Decreased appetite	34 (46.6)	66 (61.1)	73 (64.6)	126 (35.5)	59 (16.9)	298 (46.0)
Hypomagnesaemia	12 (16.4)	57 (52.8)	50 (44.2)	95 (26.8)	58 (16.6)	214 (33.0)
Nervous system disorders	**35 (47.9%)**	**78 (72.2%)**	**69 (61.1%)**	**179 (50.4%)**	**150 (42.9%)**	**360 (55.6%)**
Headache	15 (20.5)	36 (33.3)	29 (25.7)	103 (29.0)	93 (26.6)	183 (28.2)
Psychiatric disorders	**32 (43.8%)**	**72 (66.7%)**	**82 (72.6%)**	**161 (45.4%)**	**145 (41.4%)**	**346 (53.4%)**
Insomnia	12 (16.4)	38 (35.2)	39 (34.5)	78 (22.0)	70 (20.0)	166 (25.6)
Respiratory, thoracic, and mediastinal disorders	**52 (71.2%)**	**86 (79.6%)**	**94 (83.2%)**	**219 (61.7%)**	**185 (52.9%)**	**450 (69.4%)**
Cough	27 (37.0)	27 (25.0)	41 (36.3)	71 (20.0)	44 (12.6)	166 (25.6)
Dyspnoea	23 (31.5)	26 (24.1)	41 (36.3)	63 (17.7)	44 (12.6)	153 (23.6)
Vascular disorders	**29 (39.7%)**	**64 (59.3%)**	**59 (52.2%)**	**132 (37.2%)**	**109 (31.1%)**	**283 (43.7%)**
Hypotension	21 (28.8)	46 (42.6)	38 (33.6)	66 (18.6)	50 (14.3)	171 (26.4)

Source: ISS Table 12

The patient enrolled in two studies is counted only once.

In VALOR, the assignment of patients to treatment group was based on the treatment actually received. Adverse events were coded to system organ class and preferred term using MedDRA, version 13.1.
At each level of summarization (any event, SOC, and PT), patients reporting more than one AE were counted only once. Patients reporting more than one TEAE in a particular SOC were counted once for the total SOC incidence, and patients reporting more than one for the same PT were counted only once for that PT.
[a] Includes leukaemia-associated symptoms.

AE with toxicity ≥ Grade 3

In VALOR the proportion of patients with at least Grade 3 toxicity was generally similar in the two arms although Grade 5 toxicities were more frequent for vosaroxin arm than for placebo. The profile was similar in patients above 60 years compared to overall safety population.

Grade 3 AEs that occurred with a difference in incidence of ≥ 5% higher in the vosaroxin arm vs placebo were febrile neutropenia, stomatitis, hypokalemia and bacteremia.

Grade 4 AE with the greatest differences between vosaroxin arm and placebo were neutropenia and hypokalemia.

Grade 5 AE with greatest differences in incidence between vosaroxin arm and placebo were pneumonia and sepsis.

Table 16 Incidence Grade 3 or greater TEAE in at least 5% of subjects in VALOR (safety population)

System Organ Class Preferred Term	Vosaroxin/Cytarabine N = 355 n (%)			Placebo/Cytarabine N = 350 n (%)		
	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5
Patients with any Grade ≥ 3 TEAE	334 (94.1)			295 (84.3)		
Patients with Grade 3, 4 or 5 TEAEs	133 (37.5)	151 (42.5)	50 (14.1)	140 (40.0)	129 (36.9)	26 (7.4)
Blood and lymphatic system disorders	**122 (34.4)**	**111 (31.3)**	**0**	**115 (32.9)**	**99 (28.3)**	**0**
Febrile neutropenia	163 (45.9)	4 (1.1)	0	115 (32.9)	2 (0.6)	0
Thrombocytopenia	6 (1.7)	78 (22.0)	0	8 (2.3)	79 (22.6)	0
Anaemia	72 (20.3)	6 (1.7)	0	76 (21.7)	5 (1.4)	0
Neutropenia	9 (2.5)	57 (16.1)	0	5 (1.4)	44 (12.6)	0
Gastrointestinal disorders	**100 (28.2)**	**8 (2.3)**	**2 (0.6)**	**31 (8.9)**	**3 (0.9)**	**0**
Stomatitis	48 (13.5)	6 (1.7)	0	10 (2.9)	0	0
Diarrhoea	19 (5.4)	1 (0.3)	0	7 (2.0)	0	0
Infections and infestations	**143 (40.3)**	**35 (9.9)**	**41 (11.5)**	**102 (29.1)**	**20 (5.7)**	**23 (6.6)**
Pneumonia	23 (6.5)	3 (0.8)	13 (3.7)	16 (4.6)	1 (0.3)	9 (2.6)
Sepsis	8 (2.3)	20 (5.6)	14 (3.9)	5 (1.4)	7 (2.0)	6 (1.7)
Bacteraemia	39 (11.0)	4 (1.1)	0	14 (4.0)	1 (0.3)	1 (0.3)
Investigations	**32 (9.0)**	**40 (11.3)**	**0**	**14 (4.0)**	**36 (10.3)**	**0**
Platelet count decreased	1 (0.3)	21 (5.9)	0	2 (0.6)	26 (7.4)	0
White blood cell count decreased	2 (0.6)	22 (6.2)	0	4 (1.1)	17 (4.9)	0
Metabolism and nutrition disorders	**93 (26.2)**	**19 (5.4)**	**0**	**54 (15.4)**	**5 (1.4)**	**0**
Hypokalaemia	41 (11.5)	11 (3.1)	0	19 (5.4)	2 (0.6)	0
Hypophosphataemia	25 (7.0)	3 (0.8)	0	11 (3.1)	0	0
Hyperglycaemia	18 (5.1)	1 (0.3)	0	15 (4.3)	0	0
Decreased appetite	20 (5.6)	0	0	7 (2.0)	0	0
Vascular disorders	**38 (10.7)**	**4 (1.1)**	**3 (0.8)**	**19 (5.4)**	**3 (0.9)**	**0**
Hypertension	21 (5.9)	0	0	12 (3.4)	0	0

Table 17 TEAEs Grade ≥ 3 reported by 5% ≥ patients in either treatment arm in VALOR (safety population)

System Organ Class Preferred Term	VALOR All Patients		VALOR Patients ≥ 60 Years of Age	
	Vos/Cyt N = 355	Pla/Cyt N = 350	Vos/Cyt N = 226	Pla/Cyt N = 221
Patients with a TEAE ≥ Grade 3	334 (94.1)	295 (84.3)	213 (94.2)	189 (85.5)
Blood and lymphatic system disorders	**233 (65.6)**	**214 (61.1)**	**140 (61.9)**	**138 (62.4)**
Febrile neutropenia	167 (47.0)	117 (33.4)	96 (42.5)	67 (30.3)
Thrombocytopenia	84 (23.7)	87 (24.9)	55 (24.3)	56 (25.3)
Anaemia	78 (22.0)	81 (23.1)	52 (23.0)	54 (24.4)
Neutropenia	66 (18.6)	49 (14.0)	42 (18.6)	31 (14.0)
Gastrointestinal disorders	**110 (31.0)**	**34 (10.0)**	**68 (30.1)**	**24 (10.9)**
Stomatitis	54 (15.2)	10 (2.9)	36 (15.9)	9 (4.1)
Diarrhoea	20 (5.6)	7 (2.0)	12 (5.3)	6 (2.7)
Infections and infestations	**219 (61.7)**	**145 (41.4)**	**142 (62.8)**	**94 (42.5)**
Pneumonia	39 (11.0)	26 (7.4)	24 (10.6)	18 (8.1)
Sepsis	42 (11.8)	18 (5.1)	28 (12.4)	13 (5.9)
Bacteraemia	43 (12.1)	16 (4.6)	21 (9.3)	9 (4.1)
Investigations	**72 (20.3)**	**50 (14.3)**	**42 (18.6)**	**31 (14.0)**
Platelet count decreased	22 (6.2)	28 (8.0)	14 (6.2)	18 (8.1)
White blood cell count decreased	24 (6.8)	21 (6.0)	13 (5.8)	14 (6.3)
Neutrophil count decreased	15 (4.2)	16 (4.6)	12 (5.3)	10 (4.5)
Metabolism and nutrition disorders	**112 (31.5)**	**59 (16.9)**	**72 (31.9)**	**39 (17.6)**
Hypokalaemia	52 (14.6)	21 (6.0)	33 (14.6)	15 (6.8)
Hypophosphataemia	28 (7.9)	11 (3.1)	17 (7.5)	9 (4.1)
Hyperglycaemia	19 (5.4)	15 (4.3)	11 (4.9)	9 (4.1)
Decreased appetite	20 (5.6)	7 (2.0)	14 (6.2)	3 (1.4)
Vascular disorders	**45 (12.7)**	**22 (6.3)**	**31 (13.7)**	**16 (7.2)**
Hypertension	21 (5.9)	12 (3.4)	15 (6.6)	10 (4.5)

Source: dervied from VALOR Table 32 and DRN101-0375 Table 25

Notes: Table includes all TEAEs reported at Grade 3, 4 or 5 by ≥ 5 % of patients in either treatment arm of the all patients population or the patients aged ≥ 60 years. Safety population included all patients who received any amount of study drug (vosaroxin, placebo, or cytarabine). The assignment of patients to treatment group was based on the treatment actually received. AES were coded to system organ class and preferred term using MedDRA, version 13.1. At each level of summarization, patients reporting more than one AE were counted only once.

Abbreviations: Cyt, cytarabine; MedDRA, Medical Dictionary for Regulatory Activities; Pla, placebo; TEAE, treatment-emergent adverse event; Vos, vosaroxin

Treatment-related AE

A total of 95.5% of patients who received vosaroxin reported a TEAE that was considered related to study treatment.

Treatment-emergent AEs considered related to study treatment (vosaroxin or placebo, or cytarabine) and occurring in ≥ 40% of patients in the total vosaroxin group were nausea (53.2%), diarrhoea (47.7%), and stomatitis (46.8%).

There were 94.1% of patients who had AEs related to vosaroxin or placebo and 94.2% of patients had AEs considered related to cytarabine.

TEAEs that were considered related to vosaroxin that occurred in ≥ 20% of patients: nausea (52.0%), stomatitis (46.0%), diarrhoea (45.7%), febrile neutropenia (35.3%), decreased appetite (30.4%), vomiting (29.6%), anaemia (28.7%), thrombocytopenia (27.9%), and fatigue (20.7%).

TEAEs that were considered related to cytarabine that occurred in ≥ 20% of patients: nausea (52.7%), diarrhoea (48.6%), stomatitis (44.5%), febrile neutropenia (36.5%), vomiting (30.5%), decreased appetite (29.8%), anaemia (28.5%), thrombocytopenia (25.7%), and fatigue (20.5%).

In VALOR no TEAEs related to study treatment were reported in ≥ 40% patients in placebo arm but in vosaroxin arm, nausea (50.7%), diarrhoea (46.5%) and stomatitis (43.9%) were reported. Treatment-related AEs reported by ≥ 15% of patients in either arm are summarized in table below. The profile and incidence was very similar for the total population and for patients ≥ 60 years. The incidence of treatment-related febrile neutropenia and GI toxicities were higher in the vosaroxin arm than in the placebo.

Table 18 Common Treatment-related, Treatment-emergent Adverse Events in VALOR (Reported by ≥15% of Patients in Either Treatment Arm), Safety Population

System Organ Class Preferred Term	VALOR All Patients		VALOR Patients ≥ 60 Years of Age	
	Vos/Cyt N = 355	Pla/Cyt N = 350	Vos/Cyt N = 226	Pla/Cyt N = 221
Patients with any related TEAE	331 (93.2)	305 (87.1)	208 (92.0)	194 (87.8)
Blood and lymphatic system disorders	**198 (55.8)**	**176 (50.3)**	**120 (53.1)**	**115 (52.0)**
Febrile neutropenia	123 (34.6)	84 (24.0)	72 (31.9)	50 (22.6)
Anaemia	86 (24.2)	88 (25.1)	56 (24.8)	57 (25.8)
Thrombocytopenia	79 (22.3)	81 (23.1)	50 (22.1)	51 (23.1)
Neutropenia	64 (18.0)	48 (13.7)	41 (18.1)	31 (14.0)
Gastrointestinal disorders	**289 (81.4)**	**226 (64.6)**	**179 (79.2)**	**144 (65.2)**
Nausea	180 (50.7)	129 (36.9)	114 (50.4)	76 (34.4)
Diarrhoea	165 (46.5)	69 (19.7)	105 (46.5)	52 (23.5)
Stomatitis	156 (43.9)	54 (15.4)	97 (42.9)	35 (15.8)
Vomiting	100 (28.2)	45 (12.9)	57 (25.2)	23 (10.4)
Constipation	48 (13.5)	49 (14.0)	28 (12.4)	35 (15.8)
General disorders and administration site conditions	**157 (44.2)**	**125 (35.7)**	**102 (45.1)**	**85 (38.5)**
Fatigue	71 (20.0)	52 (14.9)	47 (20.8)	29 (13.1)
Pyrexia	65 (18.3)	55 (15.7)	45 (19.9)	42 (19.0)
Metabolism and nutrition disorders	**150 (42.3)**	**80 (22.9)**	**91 (40.3)**	**56 (25.3)**
Decreased appetite	95 (26.8)	33 (9.4)	58 (25.7)	25 (11.3)
Hypokalaemia	54 (15.2)	28 (8.0)	37 (16.4)	17 (7.7)

Source: VALOR Table 33 and DRN101-0375 Table 26
Note: Table includes all TEAEs reported by ≥ 15% of patients in either treatment arm of the all patients population or the patients aged ≥ 60 years. Safety population included all patients who received any amount of study drug (vosaroxin, placebo, or cytarabine). The assignment of patients to treatment group was based on the treatment actually received. AEs were coded to system organ class and preferred term using MedDRA, version 13.1. At each level of summarization, patients reporting more than one AE were counted only once. An event was considered related if there was any reasonable possibility the event was caused by vosaroxin or cytarabine, as assessed by the investigator. Events with missing relationship were considered related.
Abbreviations: Cyt, cytarabine; MedDRA, Medical Dictionary for Regulatory Activities; Pla, placebo; TEAE, treatment-emergent adverse event; Vos, vosaroxin

The treatment-related Grade 3 and above AEs reported by ≥ 5% of patients in either treatment arm are also summarized below.

Table 19 Treatment-related Adverse Events Reported at Grade 3 or above by ≥ 5% Patients in Either Treatment Arm of VALOR, Safety Population

System Organ Class Preferred Term	VALOR All Patients		VALOR Patients ≥ 60 Years of Age	
	Vos/Cyt N = 355	Pla/Cyt N = 350	Vos/Cyt N = 226	Pla/Cyt N = 221
Patients with a TEAE ≥ Grade 3	267 (75.2)	204 (58.3)	166 (73.5)	133 (60.2)
Blood and lymphatic system disorders	**190 (53.5)**	**169 (48.3)**	**113 (50.0)**	**111 (50.2)**
Febrile neutropenia	120 (33.8)	83 (23.7)	70 (31.0)	50 (22.6)
Thrombocytopenia	74 (20.8)	79 (22.6)	47 (20.8)	50 (22.6)
Anaemia	71 (20.0)	67 (19.1)	47 (20.8)	45 (20.4)
Neutropenia	59 (16.6)	46 (13.1)	38 (16.8)	29 (13.1)
Gastrointestinal disorders	**82 (23.1)**	**19 (5.4)**	**51 (22.6)**	**14 (6.3)**
Stomatitis	51 (14.4)	8 (2.3)	33 (14.6)	7 (3.2)
Infections and infestations	**129 (36.3)**	**70 (20.0)**	**87 (38.5)**	**45 (20.4)**
Sepsis	28 (7.9)	11 (3.1)	20 (8.8)	8 (3.6)
Bacteraemia	22 (6.2)	7 (2.0)	13 (5.8)	3 (1.4)
Investigations	50 (14.1)	40 (11.4)	28 (12.4)	26 (11.8)
Platelet count decreased	19 (5.4)	24 (6.9)	11 (4.9)	14 (6.3)
White blood cell count decreased	23 (6.5)	20 (5.7)	13 (5.8)	13 (5.9)

Source: derived from VALOR Table 34 and DRN101-0375 Table 27

Notes: Table includes all treatment-related TEAEs reported at Grade 3, 4 or 5 by ≥ 5 % of patients in either treatment arm of the all patients population or the patients aged ≥ 60 years. Safety population included all patients who received any amount of study drug (vosaroxin, placebo, or cytarabine). The assignment of patients to treatment group was based on the treatment actually received. AEs were coded to system organ class and preferred term using MedDRA, version 13.1. At each level of summarization, patients reporting more than one AE were counted only once. An event was considered related if there was any reasonable possibility the event was caused by vosaroxin or cytarabine, as assessed by the investigator. Events with missing relationship were considered related.

Abbreviations: Cyt, cytarabine; MedDRA, Medical Dictionary for Regulatory Activities; Pla, placebo; TEAE, treatment-emergent adverse event; Vos, vosaroxin

Serious adverse events and deaths

Deaths

In the VALOR, 76.9% patients in the vosaroxin arm died compared with 82.3% in placebo arm (cut off 26/9/2014). The majority died of disease progression but it was reported more frequent in the placebo arm (79.5% vs 65.9%). The 30- and 60-day mortalities were similar in the two treatment arms and the majority occurred > 60 days from the last study treatment. The results for the subgroup of patients ≥60 years were similar to all patients in safety population. A summary is displayed in table below. The overall cause of death showed comparable trends among subgroups based on disease status.

AE leading to death were not required to be reported if a patient died after the end of the reporting period (up to 28 days after the last treatment) unless the event was considered related to study drug. Therefore the number of patients with documented TEAEs leading to death is lower than the number of patients who died due to events other than disease progression.

Table 20 All-cause Mortality in VALOR, Safety Population

	VALOR All Patients		VALOR Patients ≥ 60 Years of Age	
	Vos/Cyt N = 355	Pla/Cyt N = 350	Vos/Cyt N = 226	Pla/Cyt N = 221
Patients who died, n (%)	273 (76.9)	288 (82.3)	182 (80.5)	198 (89.6)
Primary cause of death, n (%)[a]				
Disease progression	180 (65.9)	229 (79.5)	127 (69.8)	160 (80.8)
Other	93 (34.1)	59 (20.5)	55 (30.2)	38 (19.2)
Not reported	0	0	0	0
Days to death, mean (SD)				
Since first dose	200.5 (179.42)	194.7 (177.08)	200.6 (180.98)	191.1 (182.40)
Since last dose	174.3 (167.48)	177.4 (166.82)	172.2 (166.14)	173.6 (172.70)
All-cause mortality, n (%)				
30-day mortality	28 (7.9)	23 (6.6)	23 (10.2)	20 (9.0)
60-day mortality	70 (19.7)	68 (19.4)	46 (20.4)	50 (22.6)
Time from last dose to death, n (%)				
≤ 30 days	42 (11.8)	35 (10.0)	29 (12.8)	29 (13.1)
> 30 and ≤ 60days	49 (13.8)	50 (14.3)	32 (14.2)	37 (16.7)
> 60 days	182 (51.3)	203 (58.0)	121 (53.5)	132 (59.7)

Source: Table 2.7.4-39 and Table 2.7.4-41
Notes: Safety population included all patients who received any amount of study drug (vosaroxin, placebo, or cytarabine).
In VALOR, the assignment of patients to treatment group was based on the treatment actually received.
Abbreviations: Cyt, cytarabine; Pla, placebo; SD, standard deviation; Vos, vosaroxin
[a] Percentages are based on the number of patients who died.

In VALOR, 14.1% (50/355 patients) in the vosaroxin arm had a TEAE that led to death compared with 7.4% in placebo (26/350) and pneumonia and sepsis were the most commonly reported in both arms. A similar profile was seen in patients ≥60 years.

Seven patients in the vosaroxin arm (2.0%) died of fungal infection (5 patients on antifungal prophylaxis) compared with none in the placebo. The death resulting from fungal sepsis was considered to be treatment-related.

Table 21 Incidence of Serious Adverse Events Leading to Death (VALOR- Safety Population)

	Vosaroxin/Cytarabine N = 355	Placebo/Cytarabine N = 350	Total N = 705
Patients with any SAE leading to death	50 (14.1)	26 (7.4)	76 (10.8)
Cardiac disorders	**1 (0.3)**	**0**	**1 (0.1)**
Myocardial infarction	1 (0.3)	0	1 (0.1)
Gastrointestinal disorders	**2 (0.6)**	**0**	**2 (0.3)**
Caecitis	1 (0.3)	0	1 (0.1)
Colitis	1 (0.3)	0	1 (0.1)
General disorders and administration site conditions	**2 (0.6)**	**0**	**2 (0.3)**
Multi-organ failure	1 (0.3)	0	1 (0.1)
Sudden death	1 (0.3)	0	1 (0.1)
Infections and infestations	**41 (11.5)**	**23 (6.6)**	**64 (9.1)**
Pneumonia	13 (3.7)	9 (2.6)	22 (3.1)
Sepsis	14 (3.9)	6 (1.7)	20 (2.8)
Septic shock	2 (0.6)	3 (0.9)	5 (0.7)
Aspergillosis	2 (0.6)	0	2 (0.3)
Appendicitis perforated	0	1 (0.3)	1 (0.1)
Bacteraemia	0	1 (0.3)	1 (0.1)
Bronchopulmonary aspergillosis	1 (0.3)	0	1 (0.1)
Cellulitis	1 (0.3)	0	1 (0.1)
Enterobacter sepsis	1 (0.3)	0	1 (0.1)
Fungal infection	1 (0.3)	0	1 (0.1)
Fungal sepsis	1 (0.3)	0	1 (0.1)
Gastrointestinal infection	1 (0.3)	0	1 (0.1)
Infection	1 (0.3)	0	1 (0.1)
Klebsiella sepsis	1 (0.3)	0	1 (0.1)
Neutropenic sepsis	0	1 (0.3)	1 (0.1)
Pneumonia fungal	1 (0.3)	0	1 (0.1)
Pseudomonal sepsis	0	1 (0.3)	1 (0.1)
Pseudomonas infection	0	1 (0.3)	1 (0.1)
Septic embolus	1 (0.3)	0	1 (0.1)
Systemic candida	1 (0.3)	0	1 (0.1)
Nervous system disorders	**1 (0.3)**	**2 (0.6)**	**3 (0.4)**
Coma	1 (0.3)	0	1 (0.1)
Haemorrhage intracranial	0	1 (0.3)	1 (0.1)
Ischaemic stroke	0	1 (0.3)	1 (0.1)

Table 21 Incidence of Serious Adverse Events Leading to Death (VALOR- Safety Population)

	Vosaroxin/Cytarabine N = 355	Placebo/Cytarabine N = 350	Total N = 705
Respiratory, thoracic and mediastinal disorders	**2 (0.6)**	**1 (0.3)**	**3 (0.4)**
Acute respiratory distress syndrome	0	1 (0.3)	1 (0.1)
Pulmonary haemorrhage	1 (0.3)	0	1 (0.1)
Respiratory failure	1 (0.3)	0	1 (0.1)
Vascular disorders	**3 (0.8)**	**0**	**3 (0.4)**
Shock	2 (0.6)	0	2 (0.3)
Hypovolaemic shock	1 (0.3)	0	1 (0.1)

The table below shows the SAEs leading to death by disease status for patients ≥ 60 years of age. Overall, SAES in the SOC Infections and infestations appeared similar or slightly higher for patients on vosaroxin compared to placebo for patients with early relapse or refractory disease (9.1% - 11.7%). In contrast, the frequency was considerably higher on vosaroxin compared to placebo for patients with late relapse, 18.2% versus 2.4%, respectively. The highest difference was seen for pneumonia, the observed frequency was 2.4%-2.9% in all treatment arms irrespective of disease status whereas 11.4% (n=5) had pneumonia leading to death in the late relapse patients on vosaroxin/cytarabine.

Although strongly encouraged, the prophylactic use of antifungal agents was not mandated in VALOR. In addition, prophylactic treatment (antibacterial and antifungal) might have been suboptimal with regards to the type of anti-infective agents used, as fluconazole was the most common antifungal used and a fluoroquinolone was not administered for the majority of cases.

Table 22 Serious adverse events leading to death in patients treated with vosaroxin or placebo in combination with cytarabine, by disease status (Patients ≥ 60 years, safety population)

MedDRA System Organ Class and Preferred Term[a], n (%)[b]	Refractory Disease		Early Relapsed Disease		Late Relapsed Disease	
	Vosaroxin/ Cytarabine (n = 105)	Placebo/ Cytarabine (n = 102)	Vosaroxin/ Cytarabine (n = 77)	Placebo/ Cytarabine (n = 77)	Vosaroxin/ Cytarabine (n = 44)	Placebo/ Cytarabine (n = 42)
Patients with any adverse event leading to death	19 (18.1)	11 (10.8)	10 (13.0)	9 (11.7)	8 (18.2)	1 (2.4)
Gastrointestinal disorders	2 (1.9)	0	0	0	0	0
Cecitis	1 (1.0)	0	0	0	0	0
Colitis	1 (1.0)	0	0	0	0	0
General disorders and administration site conditions	0	0	1 (1.3)	0	0	0
Sudden death	0	0	1 (1.3)	0	0	0
Infections and infestations	12 (11.4)	10 (9.8)	9 (11.7)	7 (9.1)	8 (18.2)	1 (2.4)
Pneumonia	3 (2.9)	3 (2.9)	2 (2.6)	2 (2.6)	5 (11.4)	1 (2.4)
Sepsis	6 (5.7)	2 (2.0)	4 (5.2)	3 (3.9)	2 (4.5)	0
Septic shock	0	2 (2.0)	1 (1.3)	1 (1.3)	0	0
Aspergillosis	1 (1.0)	0	0	0	0	0
Appendicitis perforated	0	1 (1.0)	0	0	0	0
Bacteremia	0	1 (1.0)	0	0	0	0
Enterobacter sepsis	0	1 (1.0)	0	0	0	0
Bronchopulmonary aspergillosis	0	0	1 (1.3)	0	0	0
Fungal infection	1 (1.0)	0	0	0	0	0
Fungal sepsis	0	0	0	0	1 (2.3)	0
Neutropenic sepsis	0	0	0	1 (1.3)	0	0
Pneumonia fungal	1 (1.0)	0	0	0	0	0
Pseudomonal sepsis	0	1 (1.0)	0	0	0	0
Systemic candida	0	0	1 (1.3)	0	0	0
Nervous system disorders	1 (1.0)	0	0	2 (2.6)	0	0
Coma	1 (1.0)	0	0	0	0	0
Hemorrhage intracranial	0	0	0	1 (1.3)	0	0
Ischemic stroke	0	0	0	1 (1.3)	0	0
Respiratory, thoracic and mediastinal disorders	2 (1.9)	1 (1.0)	0	0	0	0
Acute respiratory distress syndrome	0	1 (1.0)	0	0	0	0
Pulmonary hemorrhage	1 (1.0)	0	0	0	0	0
Respiratory failure	1 (1.0)	0	0	0	0	0
Vascular disorders	2 (1.9)	0	0	0	0	0
Shock	1 (1.0)	0	0	0	0	0
Hypovolemic shock	1 (1.0)	0	0	0	0	0

Note: For each patient, multiple adverse events that map to a single MedDRA preferred term are summarized as a single adverse event. SOCs are sorted in alphabetical order. For SOC frequency counts, N (%), may represent multiple events per patient. Preferred terms within each SOC are sorted in descending order of total frequency count.

[a] Adverse events are mapped using MedDRA Version 13.1.

[b] Percentages are calculated using the total number of patients in the treatment group as the denominator.

Serious adverse events

The profile and incidence of SAEs were very similar for the total VALOR population and for patients ≥ 60 years.

More patients experienced SAEs in the vosaroxin arm than in the placebo arm (55.5% vs 35.7%).The following occurred in ≥ 5% of patients in the vosaroxin arm: febrile neutropenia (11.3%), sepsis (8.7%), bacteraemia (8.5%), and pneumonia (7.6%). The only SAE that occurred in ≥ 5% of patients in the placebo arm was febrile neutropenia (7.4%).

Table 23 Treatment-emergent Serious Adverse Events in VALOR reported by ≥ 1% patients in either treatment arm, Safety Population

System Organ Class Preferred Term	VALOR All Patients		VALOR Patients ≥ 60 Years of Age	
	Vos/Cyt N = 355	Pla/Cyt N = 350	Vos/Cyt N = 226	Pla/Cyt N = 221
Patients with any TESAE	197 (55.5)	125 (37.5)	128 (56.6)	72 (32.6)
Blood and lymphatic system disorders	**43 (12.1)**	**28 (8.0)**	**23 (10.2)**	**14 (6.3)**
Febrile neutropenia	40 (11.3)	26 (7.4)	21 (9.3)	13 (5.9)
Gastrointestinal disorders	**33 (9.3)**	**15 (4.3)**	23 (10.2)	11 (5.0)
Stomatitis	12 (3.4)	5 (1.4)	10 (4.4)	4 (1.8)
Colitis	5 (1.4)	0	3 (1.3)	0
Infections and infestations	**142 (40.0)**	**80 (22.9)**	**90 (39.8)**	**49 (22.2)**
Pneumonia	27 (7.6)	14 (4.9)	17 (7.5)	10 (4.5)
Sepsis	31 (8.7)	15 (4.3)	21 (9.3)	11 (5.0)
Bacteraemia	30 (8.5)	10 (2.9)	17 (7.5)	5 (2.3)
Pneumonia fungal	7 (2.0)	2 (0.6)	4 (1.8)	2 (0.9)
Neutropenic sepsis	9 (2.5)	7 (2.0)	7 (3.1)	4 (1.8)
Septic shock	7 (2.0)	6 (1.7)	4 (1.8)	4 (1.8)
Cellulitis	4 (1.1)	1 (0.3)	0	1 (0.5)
Staphylococcal infection	4 (1.1)	1 (0.3)	2 (0.9)	0
Tooth abscess	0	4 (1.1)	0	2 (0.9)
Urinary tract infection	0	4 (1.1)	0	2 (0.9)

Source: VALOR Table 37, DRN101-0375 Table 30

Safety population included all patients who received any amount of study drug. The assignment of patients to treatment group was based on the treatment actually received. Adverse events were coded to system organ class and preferred term using MedDRA, version 13.1. At each level of summarization, patients reporting more than one SAE were counted only once.

Abbreviations: Cyt, cytarabine; MedDRA, Medical Dictionary for Regulatory Activities; Pla, placebo; SAE, serious adverse event; TESAE, treatment-emergent serious adverse event; Vos, vosaroxin

Grade ≥ 3 SAE were more frequent in the vosaroxin arm (53.5% vs 32.9%) and included febrile neutropenia (11.3%), sepsis (8.7%), bacteraemia (8.5%), pneumonia (7.3%), and stomatitis (3.4%). In the placebo arm, the most commonly reported Grade ≥ 3 SAEs were febrile neutropenia (7.4%), pneumonia (4.6%), and sepsis (4.3%).

Across grades, they were more frequently reported for vosaroxin arm vs placebo: Grade 3 (31.3% vs 20.0%), Grade 4(8.2% vs 5.4%) and Grade 5 (14.1% vs 7.4%).

Treatment-related SAEs (VALOR)

More patients experienced treatment-related SAEs in the vosaroxin arm than in the placebo arm (32.7% vs 16.6%) and the majority were associated with infections (primarily sepsis, bacteraemia, neutropenic sepsis, and pneumonia). The profile and incidence was very similar for the total population and for patients ≥ 60 years of age.

The only treatment-related SAEs reported by > 5% of patients in either arm were febrile neutropenia and sepsis.

Table 24 Treatment-related Serious Adverse Events in VALOR reported by ≥ 1% patients in either treatment arm, Safety Population

System Organ Class Preferred Term	VALOR All Patients		VALOR Patients ≥ 60 Years of Age	
	Vos/Cyt N = 355	Pla/Cyt N = 350	Vos/Cyt N = 226	Pla/Cyt N = 221
Patients with any treatment-related TESAE	116 (32.7)	58 (16.6)	74 (32.7)	34 (15.4)
Blood and lymphatic system disorders	**26 (7.3)**	**17 (4.9)**	**15 (6.6)**	**9 (4.1)**
Febrile neutropenia	24 (6.8)	15 (4.3)	14 (6.2)	8 (3.6)
Gastrointestinal disorders	**26 (7.3)**	**7 (2.0)**	**18 (8.0)**	**6 (2.7)**
Stomatitis	12 (3.4)	3 (0.9)	10 (4.4)	2 (0.9)
Infections and infestations	**72 (20.3)**	**38 (10.9)**	**49 (21.7)**	**24 (10.9)**
Sepsis	21 (5.9)	11 (3.1)	15 (6.6)	8 (3.6)
Bacteraemia	12 (3.4)	5 (1.4)	9 (4.0)	1 (0.5)
Neutropenic sepsis	9 (2.5)	6 (1.7)	7 (3.1)	3 (1.4)
Pneumonia	9 (2.5)	3 (0.9)	7 (3.1)	3 (1.4)
Septic shock	3 (0.8)	4 (1.1)	1 (0.4)	2 (0.9)

Source: VALOR Table 38 and DRN101-0375 Table 31

Safety population included all patients who received any amount of study drug. The assignment of patients to treatment group was based on the treatment actually received. Adverse events were coded to system organ class and preferred term using MedDRA, version 13.1. At each level of summarization, patients reporting more than one SAE were counted only once.

Abbreviations: Cyt, cytarabine; MedDRA, Medical Dictionary for Regulatory Activities; Pla, placebo; SAE, serious adverse event; TESAE, treatment-emergent serious adverse event; Vos, vosaroxin

Other AEs of special interest

- *Cytopenia*

In the VALOR study patients ≥ 60 years reported febrile neutropenia and neutropenia more frequently in the vosaroxin arm than in the placebo (43.4% vs 30.8% and 19.9% vs 14.9 respectively). However, anaemia and thrombocytopenia were reported at similar rates in both arms (27.0% to 30.8% for anaemia and 25.7% to 26.7% for thrombocytopenia). Across both arms, febrile neutropaenia and anaemia were in the majority of cases of grade 3 toxicity whilst neutropaenia and thrombocytopaenia were of grade 4. No cytopaenia related AEs led to discontinuation in > 1 patient in both arms or were fatal.

The median time to the nadir value of neutropaenia was the same in both treatment group (15.0 days) and the median time to recovery (time from nadir to a value ≥ 0.5 x 10^9/L) was also similar in the two groups (16.0 days for vosaroxin and 15.0 days for placebo). There was no apparent relationship

between the onset and recovery of neutropenia and the development of fungal infections, pneumonia, or sepsis.

The median time to the nadir value of thrombocytopaenia was the same in both arms (15.0 days) and the median time to recovery (time from nadir to a value ≥ 30 x 10^9/L) was longer in the vosaroxin group (10.0 days) than in the placebo (8.0 days).

The median time to the nadir value of anaemia was the same in both arms (15.0 days). The median time to recovery (time from nadir to a value ≥ 80 g/L) was also the same in the two arms (8.0 days).

Results for patients ≥ 60 years of age were generally consistent with those seen for all patients. The median time to the nadir in ANC counts, platelet counts and hemoglobin levels was 15 days in both treatment groups for all three parameters. The median time to recovery (vos vs placebo) for ANC was 16 days vs 12 days, for platelets was 10 days vs 8 days, and for hemoglobin was 8 days in both arms.

- *Infection*

In the VALOR study infections were reported at higher incidence in vosaroxin arm than placebo, for the overall population and the subgroup of patients ≥ 60 years. The majority of the events were of grade 3.

For patients ≥ 60 years in VALOR, sepsis [grade ≥ 3 aggregated term], bacteraemia, Staphylococcal bacteraemia, pneumonia, and fungal pneumonia were each reported more frequently in the vosaroxin arm vs placebo.

Overall, 19 SAEs of fungal infection were reported in vosaroxim arm in VALOR (12 of which were in patients ≥ 60 years of age) compared with 9 for patients in placebo arm (8 of which were in patients ≥ 60 years of age).

Six patients ≥ 60 years of age (2.7%) in the vosaroxin/cytarabine arm of the VALOR study experienced fungal infections that led to death but only one of these fungal infections was considered to be related to vosaroxin.

- *Gastro-intestinal*

Stomatitis, nausea, diarrhoea, and vomiting were also common and more frequently reported in VALOR patients ≥ 60 years of age in the vosaroxin arm than in the placebo (49.1% versus 18.6% for stomatitis, 61.5% versus 45.7% for nausea, 71.2% versus 38.9% for diarrhoea, and 34.1% versus 19.9% for vomiting). These events were generally toxicity Grade 1 or 2 except for stomatitis, where Grade 3 events were reported for VALOR patients aged ≥ 60 years (13.7% for vosaroxin/cytarabine versus 4.1% for placebo/cytarabine) and Grade 4 (2.2% versus 0.0%, respectively). None of these AEs led to discontinuation or were fatal.

- *Metabolic-related events*

The metabolic-related events (hypokalaemia, hypomagnesaemia, hypophosphatemia, and hypocalcaemia) occurred at a higher frequency in VALOR patients ≥ 60 years of age in the vosaroxin arm than in the placebo, and may represent secondary effects of the gastro-intestinal adverse events. The majority of these events were of toxicity Grade 1 or 2.

Similar outcome was reported for overall safety population in VALOR.

- *Cardiotoxicity*

There was no apparent difference in the incidence of cardiac events of special interest between the two arms in VALOR and they were reported with low incidence. No specific cardiac AE was reported ≥ 1% patients in the vosaroxin arm and none were fatal or led to discontinuation.

An ECG and PK substudy (study DRN101-0367) was conducted as part of the VALOR study at a subset of study sites to evaluate the effect of study treatment on cardiac repolarization in a subset of patients in each treatment group during the first cycle of the treatment regimen (Induction 1). Only 25 patients (4 sites) were enrolled and 21 of these patients (9 vosaroxin group and 12 in the placebo) were included in the cardiac safety analysis.

Cardiac exclusion criteria included left ventricular ejection fraction (LVEF) < 40% by MUGA or echocardiogram and history of myocardial infarction, unstable angina, cerebrovascular accident, or transient ischemic attack within 3 months before randomization.

On Days 1 and 4 of Induction 1, digital 12-lead ECGs were recorded continuously using a Holter monitor before each treatment administration through 23 hours after the start of study treatment administration. The results revealed no clinically significant effect of vosaroxin on HR and no evidence of any effect on atrioventricular conduction or cardiac depolarization as measured by the PR interval and QRS durations. There was no effect on cardiac repolarization. There were rare morphological changes of uncertain clinical relevance that were transient and were unlikely to be related to therapy.

In addition, ECG data was recorded in study SPO-0004 but no clinically significant changes were reported.

As of 15th November 2014 no clinical symptoms of QTc prolongation, such as torsade de pointes, had been reported for any of the 932 patients who received vosaroxin across all studies.

- *Photosensitivity*

Photosensitivity reactions were reported in 2 patients during treatment with vosaroxin neither of which were considered treatment-related. Vosaroxin was found phototoxic in an in vitro assay. The SmPC recommends that patients should not expose themselves unnecessarily to strong sunlight or to artificial ultraviolet (UV) rays from Days 1 to 7 of each treatment cycle.

Laboratory findings

Haematology

In VALOR study the majority of patients had low values for haemoglobin, white blood cell, and platelet counts both at baseline and during study treatment. There was a greater decrease from baseline in median blasts cell count in the vosaroxin arm than in the placebo. Also a greater decrease in post-treatment neutrophil count from baseline was observed in the vosaroxin arm after the first study dose and neutrophil counts remained lower with vosaroxin regimen throughout Induction 1. No differences in platelets and haemoglobin were observed between baseline and post-treatment values.

There were no clinically meaningful differences between treatments in post-baseline shifts in laboratory toxicity grades.

Serum chemistry

In VALOR study, a higher number of electrolyte abnormalities were observed in the vosaroxin arm but it was not associated with an increased cardiotoxicity. Shifts in toxicity grades after study treatment were generally similar except for hypokalaemia, elevated alkaline phosphatase, hyperglycaemia, and hyponatraemia.

Table 25 Incidence of Grade ≥ 3 Treatment-Emergent Metabolic and Cardiac Adverse Events of Special Interest by Grade and Treatment (VALOR study- Safety Population)

n (%)	Vosaroxin/Cytarabine N = 355 n (%)			Placebo/Cytarabine N = 350 n (%)			Total N = 705 n (%)		
	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5
Metabolic events of special interest									
Hypokalemia	41 (11.5)	11 (3.1)	0	19 (5.4)	2 (0.6)	0	60 (8.5)	13 (1.8)	0
Hypophosphataemia	25 (7.0)	3 (0.8)	0	11 (3.1)	0	0	36 (5.1)	3 (0.4)	0
Hypocalcemia	11 (3.1)	2 (0.6)	0	5 (1.4)	1 (0.3)	0	16 (2.3)	3 (0.4)	0
Hyponatremia	8 (2.3)	0	0	8 (2.3)	0	0	16.0 (2.3)	0	0
Hypoalbuminemia	6 (1.7)	0	0	2 (0.6)	0	0	8 (1.1)	0	0
Hypomagnesaemia	1 (0.3)	0	0	0	0	0	1 (0.1)	0	0
Cardiac events of special interest									
Cardiomyopathy	1 (0.3)	0	0	1 (0.3)	0	0	2 (0.3)	0	0
Cardiac failure congestive	0	0	0	1 (0.3)	0	0	1 (0.1)	0	0
Left ventricular dysfunction	1 (0.3)	0	0	0	0	0	1 (0.1)	0	0
Ejection fraction decreased	0	0	0	0	0	0	0	0	0

The Safety population was defined as all patients who received any study medication (vosaroxin, placebo, or cytarabine). For each patient, multiple adverse events that mapped to a single MedDRA Preferred Term were summarized as a single adverse event to which the maximum CTCAE grade were assigned. System organ class frequency counts may represent multiple events per patient and were counted at the highest grade. Percentages were calculated using the total number of patients in the treatment arm as the denominator.

MedDRA version 13.1 was used.

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse events

Vital signs

No clinically significant changes in vital signs were reported across safety population in haematology malignancy studies.

Safety in special populations

- *Age*

The overall proportion of patients with TEAEs did not differ between patients < 60 years and ≥ 60 years and the types of TEAEs reported were generally similar in the two subgroups. Vomiting was reported less frequently in the ≥ 60 years (37.2% versus 45.3%) and diarrhoea and decreased

appetite were reported more commonly in the ≥ 60 years (70.6% versus 64.6% for diarrhoea and 48.4% versus 41.0% for decreased appetite).

The proportion of patients with SAEs was higher for the ≥ 60 year versus < 60 years (58.7% and 47.6%, respectively) but no individual SAE occurred with a difference of at least 5% between the subgroups. Safety data was consistent across age group of 65-74 years, 75-84 years, or ⩾ 85 years.

- *Gender*

No relevant differences were observed by gender upon exposure to vosaroxin.

- *Race*

There were 46 black or African American patients, 494 white patients and 50 patients of other races in haematology malignancy studies. Race was not reported for 58 patients.

No relevant differences were observed by race upon exposure to vosaroxin. These results should be interpreted with caution because of the disparity in sample sizes between the two groups.

- *Pregnancy and lactation*

There are no data regarding the use of vosaroxin in pregnant women. Studies in animals have shown reproductive toxicity. Vosaroxin must not be used during pregnancy and in women of childbearing potential not using contraception.

It is unknown whether vosaroxin or its metabolites are excreted in human milk. A risk to the suckling child cannot be excluded. Vosaroxin should not be used during breast-feeding.

No human data on the effect of vosaroxin on fertility are available. Studies in animals have not shown adverse effects on fertility apart from an increase in post-implantation loss with a reduction in viable foetuses.

- *Liver impairment*

No data in patients with liver impairment have been submitted.

- *Renal impairment*

No data in patients with renal impairment have been submitted.

Immunological events

None

Safety related to drug-drug interactions and other interactions

No significant drug-drug interaction was identified between vosaroxin and cytarabine in clinical studies. No other clinical drug-drug interaction studies have been conducted.

Discontinuation due to AES

A total of 18 patients in VALOR developed AEs that led to treatment discontinuation (2.3% vosaroxin vs 2.9% placebo). Of these, 4 patients developed a Grade 3 or greater TEAE leading to drug discontinuation in the vosaroxin arm compared with 8 patients in the placebo. Sepsis was the only TEAE that led to discontinuation from treatment in > 1 subject in both treatment arms. Results in patients ≥ 60 years of age were similar (1.8 % vosaroxin vs 2.3% placebo).

Table 26 Incidence of Treatment-Emergent Adverse Events Leading to Treatment Discontinuation (VALOR Safety Population)

System Organ Class Preferred Term	Vosaroxin / Cytarabine N = 355 N (%)	Placebo / Cytarabine N = 350 N (%)	Total N = 705 N (%)
Patients with Any Adverse Event Leading to Treatment Discontinuation	8 (2.3)	10 (2.9)	18 (2.6)
Blood and lymphatic system disorders	**1 (0.3)**	**1 (0.3)**	**2 (0.3)**
Thrombocytopenia	1 (0.3)	1 (0.3)	2 (0.3)
Gastrointestinal disorders	**0**	**1 (0.3)**	**1 (0.1)**
Ascites	0	1 (0.3)	1 (0.1)
General disorders and administration site conditions	**1 (0.3)**	**0**	**1 (0.1)**
Pyrexia	1 (0.3)	0	1 (0.1)
Hepatobiliary disorders	**1 (0.3)**	**0**	**1 (0.1)**
Biliary colic	1 (0.3)	0	1 (0.1)
Infections and infestations	**3 (0.8)**	**4 (1.1)**	**7 (1.0)**
Sepsis	3 (0.8)	2 (0.6)	5 (0.7)
Neutropenic sepsis	0	1 (0.3)	1 (0.1)
Systemic candida	0	1 (0.3)	1 (0.1)
Investigations	**1 (0.3)**	**2 (0.6)**	**3 (0.4)**
Alanine aminotransferase increased	1 (0.3)	1 (0.3)	2 (0.3)
Transaminases increased	0	1 (0.3)	1 (0.1)
Musculoskeletal and connective tissue disorders	**1 (0.3)**	**1 (0.3)**	**2 (0.3)**
Back pain	0	1 (0.3)	1 (0.1)
Neck pain	0	1 (0.3)	1 (0.1)
Pain in extremity	0	1 (0.3)	1 (0.1)
Pain in jaw	1 (0.3)	0	1 (0.1)
Nervous system disorders	**0**	**2 (0.6)**	**2 (0.3)**
Ischaemic stroke	0	1 (0.3)	1 (0.1)
Neurotoxicity	0	1 (0.3)	1 (0.1)

Notes: For each patient, multiple adverse events that mapped to a single MedDRA Preferred Term were summarized as a single adverse event. SOCs are sorted in alphabetical order. SOC frequency counts, N (%), may represent multiple events per patient. Preferred terms within each SOC are sorted in descending order of total frequency count. Percentages were calculated using the total number of patients in the treatment arm as the denominator.

MedDRA version 13.1 was used.

Post marketing experience

There is no post-marketing experience. Vosaroxin had not been authorised in any country at the time of submission of this application.

3.3.9. Discussion on clinical safety

Vosaroxin safety data has been provided from 648 patients with haematology malignancies that were exposed to vosaroxin. The safety evaluation is focused primarily on the pivotal study VALOR with 355 patients exposed to vosaroxin combination with cytarabine at the proposed dose and schedule compared to 350 patients exposed to cytarabine (with placebo). Data analysed in 447 patients in VALOR with ≥ 60 years further supports the proposed indication for patients 60 years and above. Few more patients in vosaroxin arm of VALOR received induction and consolidation treatment than in the control but majority (55% vosaroxin arm vs 69% placebo arm) received Induction 1 only.

Overall, the safety database is considered sufficient for assessment.

More patients in vosaroxin arm in VALOR completed the treatment (11.3% vosaroxin vs 5.1% control) and the study compared to the control. Therefore the duration of exposure to study drug in the VALOR safety population was longer for vosaroxin arm (mean duration 30 days vs 21 days/ median duration 6 days vs 5 days). There were very few dosing delays or dose adjustments in the VALOR study and overall the pattern of dose delays and adjustments was very similar in the two treatment groups.

AEs were reported for almost all patients who received vosaroxin in hematologic malignancy studies.

Cytopaenias (febrile neutropenia, anaemia, neutropenia, and thrombocytopenia) were commonly reported in all patients but neutropaenia, and especially febrile neutropaenia were more frequently reported in vosaroxin arm (48% vosaroxin vs 34% control). In the study a higher percentage of patients treated with vosaroxin/cytarabine compared with control reported GI symptoms (diarrhoea, nausea, stomatitis, vomiting), metabolic symptoms (hypokalaemia, decreased appetite, hypomagnesaemia) and abdominal pain. It is likely metabolic AE may be subsequent to vomiting and diarrhoea. Serious AE of febrile neutropaenia, infections (pneumonia, bacteraemia, sepsis) and stomatitis also occurred at a higher incidence in vosaroxin arm, the majority of Grade 3 or higher. Cytopaenias, GI symptoms, fatigue and decreased appetite were also treatment related AE of higher incidence in vosaroxin arm.

The percentage of VALOR patients with AEs leading to death was higher in the vosaroxin arm than in the placebo (14% vs 7.4%), with infections reported as the most common AE leading to death. In particular an increased incidence of serious fungal infections was observed in vosaroxin arm (12 vs 7 reported for patients ≥ 60 years and 8 vs 1 for patients < 60 years of age), that were fatal only in some patients vosaroxin arm (6 patients ≥ 60 years and 1 patient < 60 years). However, out of the 6 patients ≥ 60 years who died of fungal infection in vosaroxin arm only one case was considered related to vosaroxin). The Applicant claims the increased severity of fungal infections may possibly be related to an effect of vosaroxin on T cell function. The median time to recovery of the cytopaenias was comparable or somewhat higher for vosaroxin compared to placebo.

Stratified analysis per disease status in patients ≥ 60 years showed that the frequencies of lethal infections were more or less comparable between treatment arms for patients with early relapse/refractory disease, but considerably higher for patients with late relapse while on vosaroxin.

Prophylaxis with antibacterial or antifungal agents was not mandatory in the protocol and the treatments used were suboptimal.

It remains to be seen whether adequate prophylaxis may improve the safety outcome, especially for those patients with late relapse who did not benefit in terms of overall survival with vosaroxin treatment.

Despite a higher incidence of SAEs leading to death, the primary cause of death in both arms of VALOR was disease progression (66% vosaroxin vs 80% placebo) and occurred mostly after at least 60 days of last dose of treatment. For the 30- and 60-day mortality the primary cause of death in the placebo arm was persistent/recurrent leukaemia, while for vosaroxin arm was an infection. The same pattern was reported across the disease type subgroups although no data is available for patients above 60 years per disease group.

Vosaroxin did not show an effect on the QTc interval in the small VALOR ECG/PK substudy and no cardiac safety signals of concern were observed. This outcome is considered an advantage over other commonly used and effective treatments in AML, in particular anthracyclines but also other topoisomerase II inhibitors. However, long term safety data is missing.

Overall the profile in patients ≥ 60 years of age was very similar to that for the total population in VALOR although more deaths due to fungal infections occurred in this subgroup of patients compared to younger group.

No concerns were observed on renal, hepatic, neurologic, or pulmonary systems.

Safety and efficacy of the product have not been established in children aged less than 18 years.

3.3.10. Conclusions on clinical safety

The main safety findings of adding vosaroxin to cytarabine appeared related to cytopaenias, infections, and GI effects. Infections are the main cause of AE leading to death, with a particular increase in fungal infections in patients ≥ 60 years that needs appropriate supportive care.

The apparent lack of cardiac toxicity may represent an advantage over other topoisomerase II inhibitors, in particular anthracyclines. It is important to remember AML standard treatment (anthracycline + cytarabine) carries significant toxicity which is accepted given its known efficacy.

The number of patients reporting an adverse event leading to death, was twice as high among the patients in the vosaroxin/cytarabine arm, compared to the patients in the placebo/cytarabine arm (16.4% vs. 9.5%; a difference 6.9% for patients ≥ 60 years, and a difference 6.7% in the total population). This increase is mainly caused by the increased infection rate, due to the strong myelosuppressive effect of the combination. An increased risk of infections is especially seen within the group of patients with late relapse while on vosaroxin. Within this group, an effect on OS compared to placebo/cytarabine was not observed in contrast to patients with early relapse/refractory disease. It cannot be excluded that this is (partly) related to the increased toxicity and this at present remains a major concern. The Applicant should further discuss how this increase in mortality relates to the benefit-risk of vosaroxin for in particular the late relapse patients

Further justification that adequate anti-microbial prophylaxis could improve the safety outcome and impact on OS for patients ≥60 years with late relapse is required

3.4. Risk management plan

Safety Specification

The applicant identified the following safety concerns in the RMP:

Table 27 Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	Myelosuppression Severe infections Stomatitis and mucositis Severe diarrhoea Hypokalaemia
Important potential risks	Cardiomyopathy Tumour lysis syndrome
Missing information	Reproductive and development toxicity Use in patients with severe renal impairment Use in patients with severe hepatic impairment Use in untreated AML Use in paediatric patients Use in AML with CNS involvement Use in non-white patients

The summary of safety concerns is satisfactory.

Pharmacovigilance Plan

Table 28 Table of On-Going and Planned Additional PhV Studies/Activities in the Pharmacovigilance Plan

Activity/Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status Planned, started,	Date for submission of interim or final reports (planned or actual)
VALOR (VOS-AML-301) Observational follow-up Category 3 study	To evaluate survival in patients with first relapsed or refractory AML treated with vosaroxin/ cytarabine versus placebo/ cytarabine	Adverse reactions experienced by patients included in the study whilst being evaluated for survival	The VALOR study was database locked on 26th September 2014 (Date of Database Lock for Primary Analysis) From 27th September 2014 long-term follow-up in the VALOR study has been ongoing	Final report is expected in Q1 2018

*Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

The PhV plan has been updated and is considered acceptable, provided no further changes are required based on the CHMP assessment/opinion. However, the table in section III.5.1 needs to be updated with information on the safety concerns addressed.

Risk minimisation measures for Qinprezo

No additional risk minimisation measures have been proposed for any of the safety concerns. Routine risk minimisation is considered acceptable. Thus, Table V.3 has been omitted.

Public summary of the RMP

The public summary of the RMP requires revision as follows.

In sections VI.2.1 (Overview of disease epidemiology) and VI.2.2 (Summary of treatment benefits) the wording relating to Qinprezo/vosaroxin being 'new' should be deleted. Otherwise the public summary is considered acceptable.

3.5. Pharmacovigilance system

The CHMP considers that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

3.6. New active substance status

Based on the review of the data, the CHMP considers that the active substance, vosaroxin, contained in the medicinal product, Qinprezo, is to be qualified as a new active substance in itself.

4. Orphan medicinal products

According to the conclusion of the COMP (Opinion dated 8/03/2012) the prevalence of the "condition" acute myeloid leukaemia is 0.8 per 10000 individuals in the EU.

Vosaroxin received orphan designation for the treatment of acute myeloid leukaemia on 26th April 2012 (EU/3/12/990).

5. Benefit risk assessment

5.1. *Therapeutic Context*

5.1.1. Disease or condition

The Applicant has applied for Qinprezo (vosaroxin), in combination with cytarabine, for the treatment of adult patients ≥ 60 years with relapsed or refractory AML.

AML causes death within weeks if left untreated and the mortality rate increases dramatically with increasing age with 5-year survival rates of 3% to 8% in patients ≥60 years.

5.1.2. Available therapies and unmet medical need

There is no current standard of care regimen for the treatment of relapsed and refractory AML, and cytarabine alone or in combination regimens (e.g., with anthracyclines) remain the most commonly used treatment options. Currently there are no approved therapies in the EU specifically for the treatment of relapsed or refractory AML.

5.1.3. Main clinical studies

Efficacy is based on a single phase III randomized study (VALOR) that compared vosaroxin +cytarabine *versus* cytarabine +placebo in 711 AML adult patients in first relapse or refractory.

5.2. *Favourable effects*

- Improvement in median OS (+ 1.4 months) with vosaroxin regimen in ITT.
- In a pre-planned analysis of patients ≥ 60 years age (n=451), a greater median OS benefit (+ 2.1 months) was observed compared to the full ITT population (median OS 7.1 months vs 5.0 months; HR 0.75, p = 0.0030).
- The OS benefit in patients ≥ 60 years age remains with long term follow up (up to 48 months follow up)

- Secondary/tertiary endpoints are in favour of vosaroxin regimen in the ITT and in subpopulation of patients ≥ 60 years.
- Unlike other topoisomerase II inhibitors (e.g. anthracyclines), no evidence of cardiac toxicity has been reported.

5.3. Uncertainties and limitations about favourable effects

- The study failed its primary analysis (un-stratified median OS in ITT population 7.5 months active versus 6.1 months control; HR 0.87, p 0.061, below the pre-specified statistical significance p of 0.0494).
- Using a stratified analysis the statistical significant difference in median OS (p value 0.0242) in ITT population is not considered compelling for an application based on a single pivotal study in line with CHMP guideline (Points to consider on application with 1. Meta-analyses 2. One pivotal study - CPMP/EWP/2330/99).
- Subgroup analysis reveal patients with late relapse do not benefit from vosaroxin regimen (HR around 1). Patients with refractory or early relapse benefit from vosaroxin, with more pronounced effect in patients ≥ 60 years (OS - HR 0.73 for refractory; HR 0.61 for early relapse).
- Age was a pre-specified stratification factor but the subgroup analysis by age (cut-off 60 years) was not pre-specified for confirmatory testing.
- No clear rationale for differences observed in OS per disease status (refractory/early relapse/late relapse).The statistical significant difference in CR in favour of vosaroxin for patients in late relapse (ITT or subgroup above 60 years age) was not correlated with improved OS.
- No significant benefit with vosaroxin in patients < 60 years was seen with vosaroxin which may be due to difference in the biology of the disease with literature reports of increased drug resistance in older population. No replication data of the subgroup finding is available (draft CHMP guideline on the investigation of subgroup in confirmatory clinical trials - EMA/CHMP/539146/2013).
- Sensitivity analysis for OS censored for subsequent transplantation or subsequent treatment was in line with primary analysis. Both arms were balanced for subsequent transplant. Subsequent transplantation is not a clear answer for observed difference in OS in subgroups analysis. Having vosaroxin does not appear to increase the likelihood of undergoing subsequent transplant. Subsequent transplant was reported more frequent in younger patients and those with late relapse and may be a confounding factor, but this has not been convincingly demonstrated by the Applicant..
- No direct comparative data on OS are available when cytarabine is used in combination with other cytotoxic drugs (e.g. the FLAG-IDA or MEC regimen).
- Lack of long term safety data with regards to cardiac toxicity, but not very relevant in a disease with expected short survival.

5.4. *Unfavourable effects*

- Increased myelosuppression, especially neutropaenia and increased risk for febrile neutropaenia.

- Increase reporting of gastro-intestinal symptoms (diarrhoea, nausea, stomatitis, vomiting), metabolic symptoms (hypokalaemia, decreased appetite, hypomagnesaemia) and abdominal pain.
- Increased serious AE of febrile neutropaenia, infections (pneumonia, bacteraemia, sepsis) and stomatitis.
- Infections (especially fungal) are the most common cause of AEs leading to death in vosaroxin regimen.

5.5. *Uncertainties and limitations about unfavourable effects*

- Increased treatment-related mortality with vosaroxin, mainly due to infections, may partly be due to suboptimal anti-microbial prophylaxis
- Death to infections was higher in the subgroup of patients with late relapse which might have impacted the lack of OS benefit with vosaroxin.

5.6. *Effects Table*

Table 29. Effects Table for Vosaroxin in combination with cytarabine in patients ≥ 60 years with relapsed or refractory AML (data cut-off: 26/9/2014).

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence
Favourable Effects					
Improved median OS ITT (n=711)	Unstratified HR 0.87 (0.73, 1.02) p = 0.061	Month (diff) +1.4	7.5 m (6.4, 8.5)	6.1 m (5.2, 7.1)	• Failed primary endpoint (OS unstratified analysis) • Statistical significance only in stratified analysis • Level statistical significance not sufficient in application based on single pivotal study • Increment in median OS is clinically modest (+1.4 m) • Results driven by subgroup of patients > 60 years Rate of transplantation balanced between arms (ITT and across subgroups). Transplant is likely a cofounder factor. • No evidence of benefit in subgroup of “late relapse” patients despite statistically significant difference CR for vosaroxin. May be partly due to higher rate of subsequent transplant and partly due to higher fatal infections in vosaroxin arm.
	Stratified HR 0.83 (0.70, 0.98) p = 0.024				
	Censored for subsequent transplant HR 0.81 p = 0.024	+1.4	6.7 m	5.3 m	
	Late relapse HR 0.98 (0.66, 1.46) p = 0.96		14.1 m	12.3 m	
Improved median OS patients ≥ 60 y (451/711)	HR 0.75 p = 0.003	+2.1	7.1 m (5.8, 8.1)	5.0 m (3.8, 6.4)	• Subgroup analysis based on stratification factor but not pre-specified for confirmatory testing • Different biology of disease between younger and older patients may explain the different outcome by age but no other data replicating this finding • Consistent results with OS data on long term follow up • As for overall population
	Censored for subsequent transplant HR 0.75 p = 0.0086	+1.7	6.7 m	5.0 m	
	Late relapse HR 1.06		9.2 m (7.0, 17.3)	9.8 m (7.6, 14.3)	

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence
	(0.65, 1.72)				• Subgroup late relapse no evidence of benefit as in overall population.
Improved CR (ITT)	P<0.0001		30%	16%	• Improved CR across strata except subgroup< 60 years (27% vs 21%; p= 0.24) • No statistically significant difference in duration of CR (LFS: HR 0.89, p 0.62)
Improved Median EFS (ITT)	HR 0.67 P< 0.0002	month	1.9	1.3	No major uncertainty
No evidence of cardiac toxicity					• No cardiac toxicity reported in safety data • No signal of cardiac concern in ECG substudy • Lack of long term safety data not very relevant as survival prognosis is very short
Unfavourable Effects					
Myelosuppression Febrile neutropaenia Neutropaenia		%	 48 20	 34 15	The higher rates of infections with vosaroxin (especially fungal fatal infections) may be partly due to suboptimal anti-microbial prophylaxis but also due to longer exposure to study drug compared to control. Increased fatal infections in late relapse subgroup that may impact on OS
GI Diarrhoea Nausea Vomiting Stomatitis			 69 61 38 49	 35 48 21 19	
Infections ≥ grade 3 Grade 5			 62 11.5	 41 7	
Hypokalaemia			50	30	

Notes: Results from VALOR study

5.7. Benefit-risk assessment and discussion

5.7.1. Importance of favourable and unfavourable effects

There is no current standard of care regimen for the treatment of relapsed and refractory AML, and cytarabine alone or in combination regimens (e.g., with anthracyclines) remain the most commonly used treatment options.

Vosaroxin is a topoisomerase II inhibitor with a well-defined mechanism of action that differs from currently used topoisomerase II inhibitors like anthracyclines. It is a not substrate for the P-gp efflux transporter and it can induce apoptosis independent of p53. Therefore, vosaroxin may evade two common mechanisms of drug resistance. In addition, significant production of free radical formation,

reactive oxygen species (ROS), toxic metabolites, DNA crosslinks, or DNA alkylation are not associated with its stable core quinolone structure. Therefore, vosaroxin may avoid cumulative cardiotoxicity.

Anticancer activity of vosaroxin has been shown in combination with cytarabine in patients with relapsed/refractory AML. The median OS is 7.5 months for the overall population and 7.1 months for patients ≥60 years. The difference in median overall OS compared to placebo/intermediate dose cytarabine is modest at 1.4 month for ITT population but increases to a clinically meaningful 2.1 months in the subgroup of patients ≥60 years. The proposed indication concerns the subgroup of patients ≥60 years in a disease with median age of diagnosis of 68 years. Few improvements have been achieved in the treatment of this disease in the last decades and survival expectance remains very poor. The survival benefit is maintained with long term follow up.

A major concern was raised on the fact that the overall difference in median OS is not compelling for an application based on a single (negative) pivotal study and that the subgroup was not pre-specified for confirmatory testing. Within their response the applicant justified that the subgroup of ≥60 years is a well-defined population regarding disease characteristics and has shown to have an increased resistance to drugs. However, no replication with regards to OS of the age subgroup finding was presented and further justification is needed before a definitive conclusion can be drawn on the acceptability of the subgroup.

Additional uncertainty on the subgroup analysis is based on the lack of survival benefit in patients ≥60 years who suffer from a late relapse. Post-hoc analysis suggest that the lack of effect on OS, whereas an effect was seen on CR, may be partly explained by transplantation in the overall group although not convincingly demonstrated. On the other hand, death to infections was higher in the late relapse subgroup that might have impacted the OS as well. Although based on indirect comparisons, using data from literature suggests that the median OS seen for vosaroxin/cytarabine in the overall population is not worse than for other intensive chemotherapeutic treatments. Separate data for the subgroup <60 and ≥60 years were not provided based on literature.

The overall safety profile resembles that known from intensive chemotherapeutic treatments in AML. Higher rates of specific adverse events compared to the comparator arm might be partly explained by the use of this less intensive treatment. No cardiac toxicity was observed in both treatment arms. However, a major concern was raised on the safety of vosaroxin as treatment-related mortality was increased, mainly due to infections

Within their response, the applicant showed based on literature data the overall treatment-related mortality was in line with what can be expected from intensive treatment. However, these indirect comparisons should be interpreted cautiously given the known impact of baseline and disease characteristics on treatment-related mortality.

Post-hoc analyses stratified for disease status showed that infection rates leading to death appeared rather comparable for the early relapse and refractory elderly patient population, but were increased within the late relapse group. This difference might be partly explained by lower infection rates in the comparator arm for patients with late relapse, but this does not account for the entire difference. In this respect and assuming similar infection rates leading to death in the comparator arm as seen for early relapsed and refractory patients, frequencies of fatal infections would still be twice as high on vosaroxin/cytarabine in the late relapse group as compared to the early relapse and refractory group. Post-hoc analysis showed that antibiotic and antifungal prophylaxis might have been suboptimal within the VALOR study. The applicant therefore proposes additional warnings on the risk of serious and fatal infections within section 4.4 of the SmPC, referring to appropriate treatment guidelines and agents to be used. Although this appears reasonable, the impact of this risk minimisation strategy on both the vosaroxin/cytarabine and placebo/cytarabine arm is unknown. The applicant is asked to further

substantiate that this approach will improve the safety outcomes of vosaroxin/cytarabine in particular in the late relapse group.

5.7.2. Balance of benefits and risks

The improvement in median OS with vosaroxin (2.1 months) is not considered compelling for an application based on a single pivotal study. Although the subgroup ≥60 years can be considered a distinct patient population based on baseline and disease characteristics, the lack of replication of data regarding the difference in effect < and ≥60 years on OS and the differential effect in patients with late relapse remains of concern. Further, the increased rate of fatal infections especially in patients with late relapse remains of concern in the elderly population. The impact of the proposed risk minimization strategy needs to be further substantiated.

It should be kept in mind that only few improvements have been achieved in the treatment of this disease in the last decade and survival expectance remains very poor. No licensed treatment regimens are available and there is a need in the elderly population for effective treatments due to resistant disease and decreased tolerance for more intensive therapies. Due to a different mechanism of action vosaroxin might be effective in AML not responding to other topoisomerase inhibitors. In addition, the proposed lack of cardiac toxicity based on its mechanism of action with vosaroxin might offer an advantage in those patients reaching the maximum dose of anthracyclines or those at risk. Therefore, based on these considerations there might be a place for vosaroxin in the therapeutic armentarium to treat those elderly patients with relapsed/refractory AML that have decreased tolerance to other intensive therapies or who have already received or may not be fit for anthracycline-based regimens.

Though the unmet need and the considerations to argue that there may a place for vosaroxin in the therapeutic armentarium to treat elderly patients (≥60 years) with relapsed/refractory AML are recognized, the overall B/R of Qinprezo for this indication remains currently negative. This pertains to a lack of strong external and internal replication of the subgroup finding, whereas this is needed in the context of a (negative) single pivotal trial with inconsistent results within this age-defined subgroup not pre-specified for confirmatory testing. Furthermore, while the effect on OS between the study arms and the OS results itself in the vosaroxin/cytarabine group, if true, can be considered clinically meaningful, lack of efficacy and the increased toxicity in the sub-subgroup of patients ≥60 years with late relapse also remains of concern.

5.7.3. Additional considerations on the benefit-risk balance

N/A

5.8. *Conclusions*

The overall B/R of Qinprezo is currently **negative** and, further data, if available, and a thorough discussion on the remaining issues are needed to be able to identify the patient population best treated with the vosaroxin/cytarabine combination.