gemtuzumab ozogamicin. Quantitation of plasma concentration of hP67.6 antibody includes the antibody conjugate, the unconjugated hP67.6 antibody, and the fragments of the antibody conjugate or of the unconjugated hP67.6 antibody, which recognize the CD33 antigen. In addition, [3H]-labeled gemtuzumab ozogamicin was used in absorption, distribution, and excretion studies.

- Absorption-Bioavailability

PK parameters of single dose bolus administered by i.v. route of gemtuzumab ozogamic have been described in rats and in monkeys. Rats received either 11.2 mg protein/m^2 or 9.1 mg protein/m^2 of [3H]-labeled gemtuzumab ozogamicin in two separate studies. The highest mean concentration of total radioactivity in plasma ranged between 0.43-1 µg equiv/ml at 0.083 hours. Total clearance averaged 0.03 ml/min/kg, and mean $t_{1/2}$ and AUC values were between 81-95 hours and 18.8-22.9 µg equiv•hr/ml, respectively. In monkeys, where a dose of 16 mg protein/m^2 was administered, the bioavailability of gemtuzumab ozogamicin appeared slightly higher than in rodents. Plasma concentrations of the unconjugated calicheamicin derivatives were low, less than 2% of circulating radioactivity in plasma for up to 120 hours after dosing.

- Distribution

The distribution of gemtuzumab ozogamicin to tissues was evaluated after a single i.v. bolus of 9.1 mg protein/m^2 [3H]-labeled gemtuzumab ozogamicin in rats. Tissue samples, including blood and plasma as well as urine and faeces, were obtained up to 14 days (336 hours) after dosing. Peak concentrations of radioactivity in tissues were generally observed at the 1 or 6 hour sampling time, with lungs (0.08 µg equiv/g), liver (0.07 µg equiv/g), kidney (0.04 µg equiv/g), heart (0.04 µg equiv/g), bone marrow (0.03 µg equiv/g), and adrenals (0.02 µg equiv/g) having the highest concentrations of radioactivity from the tissues sampled. At 336 hours, concentrations of total radioactivity in these tissues declined to less than 0.01 µg/g. Tissue/plasma ratios were generally < 1, indicating that radioactivity was not extensively distributed beyond the plasma compartment. No studies were performed for plasma protein binding.

- Metabolism

The metabolism of gemtuzumab ozogamicin has been investigated in human liver microsomes (HLM), human liver cytosol (HLC) and human leukaemia cells (HL-60). A total of 11 metabolites were found after incubation with gemtuzumab ozogamicin. The biotransformation pathways identified in microsomes were hydroxylation and demethylation while the formation of NAc-epsilon calicheamicin and its derivatives appeared to be the major pathways in cytosol. Five metabolites of NAc-gamma calicheamicin DMH, including NAc-epsilon calicheamicin and its isomer, were produced from incubation in the HL-60 leukemia cells. Several common metabolites (M6, M7, and M8) were found in both liver and leukemia cell preparations.

Several common metabolites (M6, M7, and M8) were found in both liver and leukaemia cell preparations, suggesting that the metabolism of the calicheamicin into its derivatives may not be cell specific. The detection of NAc-epsilon calicheamicin and its derivatives in cells supports the hypothesis that the reactive diradical species of NAc-epsilon calicheamicin probably is formed via a glutathione-dependent reduction of the disulfide bond of NAc-gamma calicheamicin DMH within cells.
Both human liver microsomal and cytosolic metabolites were found in human hepatocytes suggesting that NAc-gamma calicheamicin DMH may be transported into human hepatocytes. CYP3A4 was identified as responsible for the oxidative metabolism of NAc-gamma calicheamicin DMH. Glutathione S-transferase (GST) was the major enzyme system involved in the metabolism of NAc-gamma calicheamicin DMH. In addition esterases and carbonyl reductase are reported to be important in the metabolism/hydrolysis of gemtuzumab ozogamicin. NAc-gamma calicheamicin and its calicheamicin metabolites were found in the urine of 4 patients receiving 9 mg/m^2 of gemtuzumab ozogamicin as a single 2-hour i.v. infusion. This suggests that NAc-gamma calicheamicin DMH may be the primary excreted hydrolytic product of gemtuzumab ozogamicin *in vivo*. Six further metabolites (M1, M5, M6, M7, M8, and M14) of NAc-gamma calicheamicin DMH were identified in urine. The main urinary metabolite was NAc-epsilon calicheamicin and its derivatives, which are expected to be inactive metabolites.

- Excretion

As part of the tissue distribution study in rats, excretion of radioactivity after administration of a single i.v. dose of [3H]-gemtuzumab ozogamicin was examined in rats. The animals received a single bolus i.v. injection of 9 mg protein/m^2 of [3H]-gemtuzumab ozogamicin. Total recovery (% dose) from urine and faeces over the 14-day period was 71%, with the majority of the radioactivity found in faeces (58.6%). These results indicate that biliary excretion and/or gastrointestinal secretion are major pathways for the elimination of [3H]-calicheamicin derivatives. The elimination rate of radioactivity was slow, with a tissue half life of 115 to 281 hours.

- Pharmacokinetic drug interaction

Studies on pharmacokinetic drug interactions were not conducted.

Toxicology

- Single dose toxicity

In rats, administration of doses from 2.8 to 84 mg/m^2 of hP67.6 protein (10 to 300 µg/kg of calicheamicin equivalent) caused lethality at doses >14 mg/m^2 of protein. The highest non-lethal dose was 9.8 mg/m^2 and the lethal dose was 28 mg/m^2 of protein. The primary causes of death were kidney and liver dysfunction. The animals were observed for a total of 14 days.
In monkeys, administration of doses from 36.9 to 73.8 mg/m^2 of hP67.6 protein (75 to 150 µg/kg of calicheamicin equivalent) caused death at doses >55.4 mg/m^2 of protein. The highest non-lethal dose was 36.9 mg/m^2 and the lethal dose 55.4 mg /m^2 of protein. The animals were observed for a total of 21 days.
In chimpanzees, 2 animals received a single 2-hour infusion of 12.5 µg/m^2 of calicheamicin derivatives or 0.5 mg/m^2 of hP67.6 antibody, which was well tolerated with no signs of toxicity evident through the 15 days post-infusion period.
Overall, administration of a single i.v. dose of gemtuzumab ozogamicin in rats, monkeys and chimpanzees led to an observed decreased in body weight and food consumption, haematologic and clinical chemistry changes.
The toxocitiy of calicheamicin derivatives have also been investigated. Gamma calicheamicin was found to be the most toxic compound, followed by gemtuzumab ozogamicin and the unconjugated NAc-gamma calicheamicin derivatives (NAc gamma calicheamicin DMH AcBut and NAc-gamma calicheamicin DMH). NAc-epsilon calicheamicin was found to be the least toxic compound.

- Repeat dose toxicity (with toxicokinetics)

Animals (rats, monkeys and dogs) were treated for a 6-cycle period (one treatment a week) after a recovery period (1 and 5 weeks). A total of 5 studies with a 6-cycle period were performed: three studies using gemtuzumab ozogamicin in rats and monkeys, and two studies using NAc-gamma calicheamicin DMH in rats and dogs.

In rats, doses of ≥10 µg/kg of gemtuzumab ozogamicin produced effects consisting primarily of clinical observations, as well as body weight, food consumption, slight anemia, and organ toxicity observed in mammary glands, kidneys, liver, and spleen. At 30 µg/kg (1.2 mg/kg or 8.4 mg protein/m^2/week), additional organs targeted by gemtuzumab ozogamicin were testes/epididymides and the bone marrow. At this dose, no reversibility of the toxic effects was observed for mammary glands, kidneys, liver and testes/ epidymides. At 3µg/kg (0.1 mg/kg or 0.7 mg protein/m^2/week), clinical observations, pathological changes, and organ weight changes were reversible by the end of the 5-week recovery period and/or were not associated with microscopic changes in the spleen and bone marrow.

The proposed no-observed-adverse-effect level (NOAL) for this study is 3 µg/kg (0.7). The maximum tolerated dose (MTD) of gemtuzumab ozogamicin used corresponded to 8.4 mg protein/m^2/week. At a dose of 0.7 mg protein/m^2/week and the MTD, the $AUC_{0-\infty}$ values for hP67.6 were 106 and 1420 µg eq•h/mL, respectively. At 8.4 mg protein/m^2/week, the $AUC_{0-\infty}$ value for total calicheamicin derivatives was 9.2 µg eq•h/mL.

Gemtuzumab ozogamicin was evaluated for toxicity in a 6-cycle study in rats (15/sex/group) at dosages of 0, 0.7, 2.8, and 8.4 mg protein/m2/week. Dosages were administered IV once weekly for 6

weeks. To evaluate potential antibody effects, a fifth group (15/sex) was given the unconjugated hP67.6 antibody in vehicle at an i.v. dose of 8.4 mg/m^2/week. There were no deaths related to the hP67.6 antibody alone. There were no hP67.6 antibody-related effects found in clinical observations, body weight, food consumption, ophthalmoscopic parameters, hematologic, clinical chemistry, urinalysis, organ weights, and in macroscopic and microscopic findings.

In monkeys, the spectrum of gemtuzumab ozogamicin toxicity was similar to that observed in rats. The NOAEL dose was 5 µg/kg of calicheamicin (corresponding to 0.2 mg protein/kg and 2.46 mg/protein/m^2). The MTD was 45 µg/kg (22.14 mg protein/m^2/week), which was the highest dose administered.

- Genotoxicity

The genotoxic potential of gemtuzumab ozogamicin was evaluated in an *in vivo* micronucleous test using cyclophosphamide as a positive control (see study design and results in table 1).

Table 1 - Gemtuzumab ozogamicin *in vivo* micronucleous test

Type of test/Study	**Test system**	**Concentrations/ Metabolising system**	**Results**
In vivo rat micronucleous test GTR 28070	CD Mice /15/sex/group	Preliminary assay: 0, 250 and 450 µg/kg Definitive assay: 00, 250, 450 and 900µg/kg	Severe toxicity in all dose groups. Significant increase in micronuclei.

Gemtuzumab ozogamicin was clastogenic in an *in vivo* mouse micronucleus assay.

- Carcinogenicity

Carcinogenicity studies were not conducted with gemtuzumab ozogamicin.

- Reproduction Toxicity

Following daily administration of gemtuzumab ozogamicin to male rats for 28 days at doses of 0.02 to 0.16 mg/kg/day (approximately 0.01 to 0.11 times the human dose on a mg/m^2 basis), gemtuzumab ozogamicin caused decreased fertility rates, reduced sperm counts and sperm motility, and an increased incidence of sperm abnormalities. These findings were attributed to primary effects on spermatogonia and spermatocytes, and did not resolve following a 9-week recovery period.
Daily treatment of pregnant rats with gemtuzumab ozogamicin during organogenesis at a dose of 0.060 mg/kg/day (approximately 0.04 times the recommended human single dose on a mg/m^2 basis) produced increased embryo-foetal mortality, and gross external, visceral, and skeletal malformations. This dose was also associated with maternal toxicity (decreased weight gain, decreased food consumption).

- Local tolerance

Local tolerance studies were not conducted with gemtuzumab ozogamicin.
Local injection sites were evaluated macroscopically in a single-dose toxicity study in rats and macroscopically and microscopically in repeat-dose toxicity studies in rats and monkeys. No compound-related findings were observed at the injection sites.

- Other toxicity studies

Immunotoxicity

Studies assessing the immunotoxicity of gemtuzumab ozogamicin were not performed.
Regarding immunogenicity after gemtuzumab ozogamicin administration, there was an antibody response to the hP67.6 antibody in the hP67.6 antibody-alone group and in gemtuzumab ozogamicin groups at $\geq$ 2.46 mg/m^2/week. At the NOAEL dose of 2.46 mg/m^2/week, the $AUC_{0-\infty}$ values for the hP67.6 antibody and total calicheamicin derivatives were 439 and 3.05 µg eq•h/mL, respectively; at a dose of 22.14 mg/m^2/week, the $AUC_{0-\infty}$ values for hP67.6 antibody and total calicheamicin derivatives were 5250 and 38.0 µg eq•h/mL.

Toxicity studies performed using the derivative NAc.gamma calicheamicin DMH in rats at 1, 10, 30 or 100 µg/kg did not provide additional information. This derivative was also tested in dogs, where 1, 5, 25, or 50 µg/kg treatments did not cause deaths. The NOAEL level for this study was 1 µg/kg.

Ecotoxicity/environmental risk assessment

An anticipated maximum of 7,500 doses per year in the EU, or 0.04 kg active protein conjugate, are expected to be administered in the next five years. This usage translates into a predicted environmental exposure concentration in the aquatic compartment of 1.3 x 10-7 µg/L, based on the CHMP guideline on environmental risk assessment of medicinal products for human use (EMEA/CPMP/SWP/4447/00, 01 Jan 2006) and does not account for patient metabolism, or the expected environmental degradation of Mylotarg via hydrolysis and photodegradation. This estimated exposure concentration is below the 0.01 µg/l threshold.

Discussion on the non-clinical aspects

Pharmacology

Gemtuzumab ozogamicin was shown to target the CD33 myeloid differentiation antigen expressed on the HL-60 promyelocytic leukaemia cell line, several other $CD33^+$ human leukaemia cell lines and on bone marrow samples from AML patients. There was no significant binding to other human tissues. The non-clinical pharmacological rationale for clinical development in the proposed orphan AML indication is supported by the non-clinical data presented.

An activity was observed in several patients that had undetectable CD33 antigen on their leukaemic blasts. This activity might be best explained by non-specific uptake of conjugate in patients whose leukaemia was highly sensitive to the effects of calicheamicin. This activity was also observed *in vitro* in a $CD33^-$ cell line, although cytotoxicity was detected at concentrations higher that seen for $CD33^+$ cell lines.

Regarding safety phamacology, no significant neurobehavioral, gastrointestinal, urinary changes were observed with gemtuzumab ozogamicin in appropriate animal models at doses consistent with the proposed human dose. No studies on pharmacodynamic drug interactions have been conducted since the claimed indication for gemtuzumab ozogamicin is for its use as single agent treatment for AML. Therefore, studies on interactions with other agents used for the treatment of AML were not required.

Pharmacokinetics/Toxicology

Both human liver microsomal and cytosolic metabolites were found in human hepatocytes suggesting that NAc-gamma calicheamicin DMH can be transported into human hepatocytes. CYP3A4 was identified as responsible for the oxidative metabolism of NAc-gamma calicheamicin DMH. However, since NAc-gamma calicheamicin DMH is transformed to other non-oxidative metabolites, inhibition of CYP3A4 is unlikely to result in significant drug-drug interactions in humans.

In rats and monkeys, the toxicity of gemtuzumab ozogamicin was dominated by cytotoxic actions on dividing cells after high doses, and by renal tubular and hepatic damage. Consistent with the known ability of calicheamicin to cause double-stranded breaks in DNA, gemtuzumab ozogamicin was clastogenic in the mouse *in vivo* micronuleus test. In reproductive toxicity studies, gemtuzumab ozogamicin was shown to affect fertility both in male and female rats. The toxic effect on male fertility has to be considered severe and not reversible, while an effect on female fertility is considered treatment-related and reversible. In the developmental toxicity studies a severe grade of embryofoetal toxicity, including several morphological anomalies, was observed at all doses tested suggesting that gemtuzumab ozogamicin is teratogenic in rat when administered i.v. during organogenesis. Gemtuzumab ozogamicin must not be used during pregnancy and in women of childbearing potential not using effective contraception, unless the potential benefits outweigh the potential risks.

Due to the absence of cross-reactivity of the hP67.6 antibody to different laboratory species, animal studies can only be of limited value as there is no binding, specific intracellular uptake, and metabolism of the antibody conjugate that underlies the therapeutic action of gemtuzumab ozogamicin in humans. The only non-clinical safety study conducted in an animal species with cross-reaction to the antibody was a study conducted in chimpanzee. Apart from changes in some blood parameters, gemtuzumab ozogamicin was well tolerated at the tested doses, albeit that the highest single dose was below the MTD.

Therefore, the safety assessment of gemtuzumab ozogamicin mainly relies on the clinical safety data since no other relevant animal species (besides chimpanzee) is available and data from a surrogate model, such as a murine model, were not submitted.

Ecotoxicity/environmental risk assessment

The estimated exposure concentration of Mylotarg is below 0.01 µg/L. At this predicted exposure level in the environment the risk is regarded as negligible. Mylotarg is not stable in aqueous solution and is degraded by light. As indicated in the labelling, toxic waste disposal procedures prescribed for anticancer drugs must be used if the product must be discarded.

2.4 Clinical aspects

The clinical programme of gemtuzumab ozogamicin comprised three phase I/II dose-finding studies (0903A1-101-US, 0903A1-102-US, and 0903A1-103-JP) and three phase II, open-label, single-arm, 3-part, multidose, multicentre clinical trials (0903B1-201-US/CA, 0903B1-202-EU, and 0903B1-203-US/EU) as a single-agent therapy. These three pivotal studies involved patients with relapsed or refractory CD33-positive AML and were conducted at 74 investigational sites in the United States, Canada, and Europe. The clinical trials were performed in accordance with GCP as claimed by the applicant. The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.
It was proposed that gemtuzumab ozogamicin is administered under the supervision of physicians experienced in the treatment of acute leukaemia and in facilities equipped to monitor and treat leukaemia patients. The proposed posology of gemtuzumab ozogamicin was 9 mg/m^2, infused over a 2-hour period. The proposed treatment course with gemtuzumab ozogamicin was a total of 2 doses, with 14 days interval between the doses. Gemtuzumab ozogamicin was not to be administered as an i.v. push or bolus. The reconstituted and diluted gemtuzumab ozogamicin solution was to be infused over a 2-hour period. Mylotarg was to be given peripherally or through a central line. There were no controlled trials demonstrating efficacy and safety using gemtuzumab ozogamicin in combination with other chemotherapeutic agents. Therefore, gemtuzumab ozogamicin would only have to be used as a single chemotherapeutic agent and not in combination chemotherapy regimens outside clinical trials

Pharmacokinetics

The pharmacokinetics of gemtuzumab ozogamicin has been investigated in a phase I dose escalation study (0903A1-101-US) in patients with relapsed or refractory acute AML, at doses ranging from 0.25 to 9 mg/m^2 and in a phase I study (0903A1-102-US) in paediatric patients with AML.
The pharmacokinetic parameters of gemtuzumab ozogamicin at the therapeutic dose (9 mg/m^2) were further studied in the three phase II pivotal studies 0903B1-201-US, 0903B1-202-EU, and 0903B1-203-EU/US (see designs, clinical efficacy section).
Enzyme linked immunosorbent assays (ELISA) and enzyme immunoassay (EIA) were used in pharmacokinetic studies of hP67.6 conjugate, both for the antibody and for calicheamicin moieties. Methods were validated in human plasma, calculating assays performance as accuracy, precision (within assay and day-to-day reproducibility), linearity, limit of quantification, stability of samples and matrix effects. Pharmacokinetics analyses were performed using standard non-compartmental analysis. ANOVA analysis using dose-corrected data was used.

- Absorption

No bioavailability or bioequivalence studies of gemtuzumab ozogamicin were conducted as the drug is administered intravenously.

- Distribution

Phase I studies demonstrated that the distribution of hP67.6 antibody decreased at the highest dose levels.
From phase II studies, the highest plasma concentration of hP67.6 antibody was observed shortly after the end of the 2-hour infusion. When pharmacokinetic analyses were performed following the second administration (14 days after the first dose) plasma concentration of hP67.6 antibody was higher. A decrease in leukaemic cells was observed after the administration of the first dose. The mean C_{max} of hP67.6 antibody following the first dose for patients who received 9 mg/m^2 gemtuzumab ozogamicin

was 3.0 mg/L, with values that ranged from 0.4 to 18.3 mg/L. The C_{max} increased to 3.6 mg/L (0.3 to 10.6 mg/L) after the second dose. The mean increase in C_{max} was approximately 20%, clinically, a small difference considering the high inter-patient variability. In agreement with these studies, a decrease in the volume of distribution at steady state (V_{SS}) of hP67.6 was observed across the first and second dose period, which is consistent with the changes seen in other pharmacokinetic parameters. V_{SS} was 18 L during the first dose period, and decreased to 10 L during the second dose period. Large inter-patient variability was also noted for the volumes of distribution with CVs of approximately 100%. The estimated volumes of distribution for hP67.6 were consistent with those estimated from preclinical biodistribution studies reported in the literature that used various radiolabeled anti-CD33 antibodies.

The C_{max} for unconjugated calicheamicin following a dose of 9 mg/m^2 of gemtuzumab ozogamicin was 0.005 mg/L.

- Metabolism

Based on various *in vitro* assays, it was found that several enzyme systems in human liver microsomes, hepatocytes, and cytosol are involved in the activation/metabolism of the non-antibody active moiety of gemtuzumab ozogamicin, NAc-gamma calicheamicin DMH. Enzyme systems involved include esterases, carbonyl reductase, and the involvement of cytochrome P450 (CYP) 3A4 in the oxidative metabolism steps.

- Elimination

Clearance (Cl) of hP67.6 antibody from plasma was 0.52 l/h after the first dose and 0.20 l/h after the second dose. The terminal half-life ($t_{1/2}$) for hP67.6 was 62 hours after the first dose and 90 hours after the second dose. The last observable $t_{1/2}$ for total calicheamicin was 41 hours following the first dose and 64 hours following the second dose. The last observable $t_{1/2}$ for unconjugated calicheamicin derivatives was 143 hours following the first dose and 104 hours following the second dose. No human data was provided that allows a quantification of excretion.

- Dose proportionality and time dependencies

The phase I dose escalation study showed that there was no dose-proportional increase in C_{max} and AUC values of gemtuzumab ozogamicin. Concentrations of hP67.6 increased as the doses of gemtuzumab ozogamicin were increased, but a definitive assessment of dose linearity was not performed due to the large between-subject variability and the small number of patients studied within the different dose-treatment groups. Between-subject variability was large for most PK parameters (see table 2). No data on within-subject variability were provided.

Table 2: Summary of between-subject CV% for studies 0903B1-201-US/CA, 0903B1-202-EU, 0903B1-203-US/EU (data for hP67.6)

Phase II study	Cmax	AUC	T½	Vz
0903B1-201	35-74%	76-88%	60-72%	95-111%
0903B1-202	51-61%	104-138%	40-175%	101-105%
0903B1-203	45-51%	79-94%	50-217%	78-90%

- Special populations

The first phase I study conducted in an adult population was not designed to examine the impact of age and sex on the pharmacokinetic parameters (PK parameters) of gemtuzumab ozogamicin.

In the phase II studies, patient age ranged from 20 through 87 years and each sex was equally proportional. A total of 259 of the 271 patents (96%) were of white race. Pharmacokinetics of gemtuzumab ozogamicin was assessed in elderly patients as a part of a phase II study. Plasma pharmacokinetics of hP67.6 and calicheamicins (total and unconjugated forms) were evaluated and there were no observed relationships between patient demographics and PK parameters for either hP67.6 or calicheamicin. Pharmacokinetic effects based on gender, body surface area, and ethnic origin were also examined but no relationship was determined.

A phase I study (0903A1-102-US) conducted in paediatric patients evaluated gemtuzumab ozogamicin doses ranging from 6 to 9 mg/m^2. PK parameters were determined for 29 patients, 22 of whom had PK parameters determined after a second dose. A consistent and statistically significant change in hP67.6 PK measurements was observed between the first and second dose period. AUC increased by 63% and 77%, with a corresponding decrease in clearance for the 6 mg/m^2 and 9 mg/m^2 groups, respectively. The volumes of distribution also decreased for all dose groups. Children receiving a 9 mg/m^2 dose had the following hP67.6 PK parameter estimates (mean ± SD): C_{max} 3.47 ±1.04 mg/L; AUC 136± 07 mg•h/L; Cl 0.12 ± 0.15 l/h/m^2; V_{ss} 6.5 ± 5.5 l/m^2; half-life 64 ± 44 h. These results are consistent with those seen in the adult population. The inter-subject variability within dose period was large for most parameters.

- Pharmacokinetic interaction studies

A limited assessment of possible drug interaction with acetaminophen, diphenhydramine, and hydroxyurea on hP67.6 pharmacokinetics was done. Most patients were pretreated with acetaminophen and diphenhydramine. The hP67.6 AUC for patients who received pre-treatment were found to be similar to those for patients who did not receive pre-treatment.

Pharmacodynamics

- Mechanism of action

Gemtuzumab ozogamicin is cytotoxic to the CD33$^+$ HL-60 human leukaemia cell line. Gemtuzumab ozogamicin produces significant inhibition of colony formation in cultures of adult leukaemic bone marrow cells. The cytotoxic effect on normal myeloid precursors leads to myelosuppression. In preclinical animal studies, gemtuzumab ozogamicin demonstrated antitumour effects in HL-60 human promyelocytic leukaemia xenograft tumour in athymic mice.

- Primary and Secondary pharmacology

In study 0903A1-101-US, saturation of the CD33 antigen by hP67.6 was evaluated with doses of gemtuzumab ozogamicin between 0.25 to 9 mg/m^2. High variability in saturation was observed when the hP67.6 AUC was less than 100 mg•h/L.

Discussion on clinical pharmacology

Based on preclinical studies it is believed that gemtuzumab ozogamicin exerts its antineoplastic effect by being internalized following binding to CD33-positive antigen on cells. However, at the clinical level pharmacodynamics of gemtuzumab ozogamicin have been scarcely documented. The selected dose of 9 mg/m^2 seems of gemtuzumab ozogamicin is associated with a high degree of CD33 saturation. Its role in effective therapy has also been shown.
The pharmacokinetics of gemtuzumab ozogamicin (the antibody hP67.6, total calicheamin and unconjugated cailcheamin) has been studied in patients only. The analytical methods used were appropriate and adequately documented, however the specificity of the hP67.6 ELISA was considered poor. The CHMP considered that the low specificity was likely to be related to the large analytical variability observed and could have influenced the interpretation of the pharmacokinetics data.

After administration of the first recommended 9 mg/m^2 dose of gemtuzumab ozogamicin, given as a 2-hour infusion, the elimination half-life of total and unconjugated calicheamicin was about 41 and 143 hours, respectively. After the second 9 mg/m^2 dose, the half-life of total calicheamicin was increased to about 64 hours, and the AUC was about twice that in the first dose period. The AUC for the unconjugated calicheamicin increased 30% after the second dose. Age, gender, body surface area, and weight did not affect the pharmacokinetics of gemtuzumab ozogamicin. The pharmacokinetics of gemtuzumab ozogamicin in paediatric patients followed the profile and variability of adult patients and mean pharmacokinetic parameters are similar to values reported in adults. Based on preclinical studies, the excretion of gemtuzumab ozogamicin was mainly through faeces, probably through the biliary excretion of metabolites. Dose proportionality could not be demonstrated.
The pharmacokinetics in special populations was scarcely studied by covariate analysis. No association with gender, age and weight was observed. No data were provided in patients with hepatic or renal impairment. Mild to moderate renal and hepatic impairment is unlikely to influence the

pharmacokinetics and pharmacodynamics of gemtuzumab ozogamicin to a clinically relevant extent. Due to lack of clinical data, caution is advised in patients with severe hepatic and renal impairment. The PK in children has been studied and the PK parameters were similar to those achieved in adults, based on a surface-area normalised dose. The clinical experience in children and adolescents is limited. Based on the information available at the time for the marketing authorisation application, 6 mg/m^2 represents a dose that is tolerable in this population (relapse paediatric patients).
No clinical drug-drug interaction studies were performed for gemtuzumab ozogamicin. *In vitro* studies in human liver microsomes, demonstrated that clinically achievable levels of gemtuzumab ozogamicin and calicheamycin do not inhibit the catalytic activity of CYP enzymes or induce the catalytic activity of CYP3A4. Clinically relevant drug interactions involving gemtuzumab ozogamicin and concomitant medicinal products that are substrates of cytochrome P450 enzymes are unlikely to occur.

Clinical efficacy

- Dose response studies

Study 0903A1-101-US: Open-label, single-arm, phase I dose-escalation study aiming at determining the MTD, the safety and tolerability and the pharmacokinetics of gemtuzumab ozogamicin in patients with AML.
Forty-one patients aged ≥16 to ≤70 years with CD33$^+$ AML who were not in remission or relapsed after remission were enrolled in the study in successive dose levels of 0.25, 0.5, 1, 2, 4, 5, 6, and 9 mg/m^2 gemtuzumab ozogamicin. Gemtuzumab ozogamicin was given as a single 2-hour i.v. infusion *per dose* with a minimum of 14 days between doses. This time interval between doses was chosen as dose clearance is expected in approximately 12 to 15 days. The chosen interval was expected to avoid accumulation, while maintaining a level of gemtuzumab ozogamicin to prevent disease recurrence.
Two patients achieved a complete response (CR). One patient received one dose of 1 mg/m^2 of gemtuzumab ozogamicin and the other received two doses of 4 mg/m^2 gemtuzumab ozogamicin. In addition, 7 patients had clearance of leukaemic blasts from bone marrow and blood (≤5%) but without full recovery of peripheral blood platelet counts. Dose was not escalated beyond 9 mg/m^2 because of myelosuppression, even though no prospectively defined dose-limiting toxicity (DLT) had been encountered. Because most patients (4 of 7) at this dose level experienced blast clearance and because CD33 saturation data suggested that a dose level of 9 mg/m^2 would effectively saturate CD33 sites in all patients regardless of leukaemia burden, 9 mg/m^2 was the dose selected for further trials.

Study 0903A1-102-US: Open-label dose-escalation study with the primary objective of determining the recommended dose, safety and tolerability of gemtuzumab ozogamicin in paediatric patients with AML.
Twenty nine paediatric patients (19 with relapsed AML and 10 with refractory AML) were enrolled in 3 ascending dose levels of gemtuzumab: 6 mg/m^2, 7.5 mg/m^2, and 9 mg/m^2. Twenty-three patients received a second dose of gemtuzumab ozogamicin, generally 14 days after the first dose. DLTs were observed in children at the 9 mg/m^2 dose: grade 3 or 4 elevations of aspartate aminotransferase (AST)/alanine aminotransferase (ALT) were observed in 3 patients and hepatic veno-occlusive disease (VOD) was seen in 1 patient. The dose of 6 mg/m^2 was selected as the recommended dose because the study was terminated before the 7.5 mg/m^2 dose level could be fully enrolled and evaluated.
Four patients achieved CR (two at 6 mg/m^2 and two at 9 mg/m^2) and 4 experienced complete remission with incomplete platelet recovery (CRp), one at 7.5 mg/m^2 and three at 9 mg/m^2, for an OR rate of 28% (8 of 29 patients) in patients ≤16 years old. Of these 8 patients, 5 were patients in first relapse and 3 were patients with refractory AML. No further analysis of paediatric efficacy was performed.

Study 0903A1-103-JP: Single-agent, multicenter, phase I/II clinical trial conducted in Japan. Patients with CD33$^+$ relapsed or refractory AML were enrolled in the two phases of the study. In phase I (dose-escalation phase) of the study, 20 patients were randomly assigned into 3 dose levels: 6.0, 7.5, and 9.0 mg/m^2 of gemtuzumab ozogamicin. The 9.0 mg/m^2 dose level was determined to be the MTD. Two of the 20 patients had CR and two had blast clearance. All four patients were treated at the 9 mg/m^2 MTD dose level. In phase II (efficacy and safety evaluation phase) of the study, patients were

treated with two doses (14 days apart) of 9 mg/m^2 gemtuzumab ozogamicin. Five of the 20 patients (25%) achieved CR and one achieved CRp (5%).

- Main studies

Three study reports (0903B1-201-US/CA, 0903B1-202-EU, 0903B1-203-US/EU) of open-label, phase II, single-arm, multidose clinical trials pertinent to the claimed indication were submitted (table 3). Because of the similarity in study designs, objectives, patient demographics, and dosing schedules, data from the three studies were pooled to attain a larger efficacy population (277 patients).

Table 3: overview of studies 0903B1-201-US/CA, 0903B1-202-EU, 0903B1-203-US/EU

Studies	Design	Purpose	Dose (mg/m^2)	Number of Sites	Patients Enrolled	Control Groups	Degree of Blinding
0903B1-**201**-US/CA	Simon 2-stage	Safety and Efficacy	9	14	84	None	Open-label
0903B1-**202**-EU	Non-comparative	Safety and Efficacy	9	24	95	None	Open-label
0903B1-**203**-US/EU	Simon 2-stage	Safety and Efficacy	9	36	98	None	Open-label

METHODS

Study Participants

The main inclusion criteria included CD33$^+$ AML patients in first relapse (>5% leukaemic blasts as determined by central flow cytometry laboratory tests) and are summarised in table 4. Patient inclusion criteria were similar for all studies. However, study 0903B1-202-EU also included patients with prior bone marrow transplant.

Table 4: Key inclusion criteria (studies 0903B1-201-US/CA, 0903B1-202-EU, 0903B1-203-US/EU)

Criteria	Study 201	Study 202	Study 203
CD33-positive AML in first relapse	Yes	Yes	Yes
Age, years	≥18	≥18	≥60
Duration of first remission, months	≥6	≥6	≥3
Prior HSCT	Not permitted	Permitted[a]	Not permitted
ECOG performance status 0 - 2, inclusive	Yes	Yes	Yes
Baseline serum creatinine	≤2.0 mg/dL (176.8 µmol/L)	≤2.0 mg/dL (176.8 µmol/L)	≤3.0 mg/dL (265.2 µmol/L)
Baseline serum total bilirubin	≤1.5 mg/dL (25.65 µmol/L)	≤1.5 mg/dL (25.65 µmol/L)	≤2.0 mg/dL (34.2 µmol/L)
No myelodysplastic syndrome	Yes	Yes	Yes
No secondary AML	Yes	Yes	Yes

a. Originally not permitted, but protocol 202 was amended to allow prior HSCT.
Abbreviations: AML = acute myeloid leukemia; ECOG = Eastern Cooperative Oncology Group; HSCT = hematopoietic stem cell transplantation.

Treatments

The treatment included three parts. Part 1, induction therapy, consisted in two doses of 9 mg/m^2 gemtuzumab ozogamicin, and a 28-day follow-up after the last dose. Part 2, consolidation and follow-up, consisted in monthly evaluation for 6 additional months. Patients who had a complete remission (CR) or a complete remission with incomplete platelet recovery (CRp) or who had clearance of blasts with gemtuzumab ozogamicin treatment were followed for efficacy and safety, and all others were followed in part 2 for safety only. In part 2 further consolidation therapy (HSCT or other chemotherapy) was allowed, 30 days after the bone marrow clearing of blasts indicating remission. In part 3, follow-up assessments of disease status and survival, all patients who achieved CR or CRp continued to be followed (contacted every 3 months by telephone) for an additional 18 month after the follow-up period and every 6 months thereafter, until time of relapse or death or date of last follow-up. Patients in remission after the first course of gemtuzumab ozogamicin were eligible for additional courses of gemtuzumab ozogamicin. Only data from the first course of gemtuzumab ozogamicin treatment for these patients are included in the efficacy analyses. Hydroxyurea use was allowed to

reduce the peripheral white blood cell (WBC) count to <30 000/µl before gemtuzumab ozogamicin use if the initial WBC count was ≥30 000/µl. Premedication with acetaminophen and an antihistamine was required for all patients. For patients responding to treatment (CR, CRp, and those with ≤5% blasts in the bone marrow and clearance of blasts from the peripheral blood), additional post-remission treatment for AML was permitted beginning 30 days after being in remission after gemtuzumab ozogamicin treatment. Post-remission therapy options included autologous HSCT, allogeneic HSCT, or additional cytotoxic chemotherapy. Patients who did not respond to gemtuzumab ozogamicin were permitted to receive other treatment as soon as lack of response was documented.

Objectives

The primary objective was to assess the efficacy (patients achieving complete remission: CR) of gemtuzumab ozogamicin. The secondary objectives were to assess the duration of CR and complete remission with incomplete platelet recovery (CRp), to assess the pharmacokinetic properties and to assess possible predictors of response.

Outcomes/endpoints

The primary efficacy endpoint was the number of patients attaining a CR. The secondary endpoints were the rates of CRp, relapse-free survival (from initial documentation of remission and post-HSCT), total survival (from first dose of study drug and post-HSCT), and time to platelet and time to absolute neutrophil count (ANC) recovery. Other efficacy endpoints included assessment of hematologic recovery, post-remission therapy, post-HSCT recovery and post-HSCT survival. Intent-to-Treat (ITT) population included all patients who were entered into the study. The modified intent-to-treat (mITT) population included those ITT patients who received at least 1 dose of gemtuzumab ozogamicin. Efficacy analyses were performed on the mITT population.

Two sets of response criteria were used: Diagnostic criteria for AML defined using the recommendations of a 1988 workshop sponsored by the National Cancer Institute, referred to in this application as "protocol-defined criteria", and diagnostic criteria for AML defined using the recommendations of a 2003 International Working Group (IWG) of investigators, referred to in this summary as "IWG-defined criteria". Remission status was determined using both the protocol-defined criteria and IWG-defined criteria (see definition in table 5).

Table 5: Comparison of IWG-defined and protocol-defined criteria for determination of remission status

	Complete Remission (CR)		Complete Remission with Incomplete Platelet Recovery (CRp)	
Criterion	**Protocol-Defined (CR)**	**IWG-Defined (CR*)**	**Protocol-Defined (CRp)**	**IWG-Defined (CRp*)**
First evaluation	28 days after last dose	7-10 days after last dose	28 days after last dose	7-10 days after last dose
% Leukemic blasts in bone marrow (aspirate or biopsy)[a]	≤5%	<5%	≤5%	<5%
Leukemic blasts in peripheral blood	----------Absent----------			
≥200 Nucleated cells, no blasts with Auer rods, no extramedullary disease, absence of a unique phenotype identical to baseline specimen	Not a criterion	Criterion [b]	Not a criterion	Criterion [b]
Platelet count	---------- ≥100 x 10^9/L ----------		---------- <100 x 10^9/L ---------	
ANC	≥1.5 x 10^9/L	>1.0 x 10^9/L	≥1.5 x 10^9/L	>1.0 x 10^9/L
Hemoglobin	≥90 g/L	Not a criterion	≥90 g/L	Not a criterion
Platelet transfusion independence	≥1 week	Yes (no duration specified)[c]	≥1 week	Yes (no duration specified)[b]
RBC transfusion independence	≥2 weeks	Yes (no duration specified)[c]	≥2 weeks	Yes (no duration specified)[b]
Effect of additional chemotherapy or HSCT	Evaluation ends	Not a criterion	Evaluation ends	Not a criterion

a: When both bone marrow aspirate and biopsy results were available, both had to be ≤5% (protocol criteria) or <5% (IWG criteria). In cases of discrepancy between local and expert blast evaluations, the expert's evaluation overruled the local investigator's evaluation; b: These criteria cannot be documented programmatically because they were not required for the per protocol analysis of remission; c: Patients with no transfusions on the date of CR* or CRp* are considered transfusion independent.; Abbreviations: ANC = absolute neutrophil count; CR = complete remission defined by protocol criteria; CR* = complete remission defined by IWG criteria; CRp = complete remission with incomplete platelet recovery defined by protocol criteria; CRp* = complete remission with incomplete platelet recovery defined by IWG criteria; HSCT = hematopoietic stem cell transplantation; IWG = International Working Group; RBC = red blood cell.

No remission (NR): Patients were considered to be in NR if they did not meet all the criteria for CR/CR* or CRp/CRp*.

Relapse-free survival (RFS) was defined only for CR and CRp and was measured in months from the date of attaining a morphologic leukaemia-free state until the date of AML relapse or death from any cause, whichever occurs first. Per protocol, the date of relapse was the date on which the investigator recorded an assessment of relapse. An IWG relapse was defined as the return of leukaemic blasts in the peripheral blood or increases in the bone marrow blasts to levels ≥5%.

Overall survival (OS) was measured for all patients from the date of first dose to the date of death. For analysis of OS by remission category, patients who did not receive at least 2 doses of gemtuzumab ozogamicin were excluded, as well as deaths that occurred before the end of part 1 (see treatment). These patients did not complete the treatment phase of the study and thus could not be evaluated for response.

Subgroup analyses were performed on the mITT population for remission, RFS, and OS. Efficacy was analysed by age group (<60 or ≥60 years), ethnic origin, sex, duration of first remission, and cytogenetic classification.

Patients who did not respond to the first dose of gemtuzumab ozogamicin were considered treatment failures and did not receive a second dose. They were discontinued from further treatment with gemtuzumab ozogamicin, but were followed up in the study. Patients in remission after the first course of gemtuzumab ozogamicin were eligible for additional courses of gemtuzumab ozogamicin. Remission categories were determined after additional courses of gemtuzumab ozogamicin, but no further efficacy analyses were conducted on this patient population.

Sample size
The assumption was made that the response probability of an ineffective drug was 0.15, with the probability of accepting an ineffective drug (α) = 0.10. The response probability of an effective drug (i.e. the target level) was chosen as 0.30, with the probability of rejecting an effective drug (β) = 0.10. Based on these assumptions, the sample size of the first stage was 23 patients and the sample size required for the entire study was 55 patients.

Randomisation and blinding (masking)
Studies 0903B1-201-US/CA, 0903B1-202-EU, 0903B1-203-US/EU were open-label studies without randomisation. However, slides of bone marrow aspirates and bone marrow biopsies were blinded to both the patient's identity and temporal order of slides before shipment to the independent pathologist for analysis.

Statistical methods
Sample size requirements and stopping rules were based on the CR rate and did not consider CRp rate nor safety profile. The designs were modified and the decision to continue the studies beyond the interim analysis was not based solely on the CR rate, but resulted from an evaluation of the composite efficacy and safety information available at the time of the interim analysis.

RESULTS

Participant flow
A total of 377 patients were screened and 277 patients were evaluated for efficacy after the pooling of studies. The overall patient disposition is summarised in table 6. Twenty-five patients were alive at the end of part 3.

Table 6: Summary of patient participation (studies 0903B1-201-US/CA, 0903B1-202-EU, 0903B1-203-US/EU)

Study /Disposition	Number of Patients
Part 1	
Enrolled and received dose 1	277
Received dose 2	210
Received dose 3	7
Died in part 1	44
Part 2	
Entered 6-month follow-up	233
Died in part 2	128
Part 3	
Entered 18-month follow-up	105
Died in part 3	80
Remain in part 3	25

Conduct of the study
Each of the studies protocol had 4 to 5 amendments, mainly on clarification points, extension of number of patients and exclusion of HIV positive patients.

Baseline data
The phase II clinical trials included adult patients between 20 and 87 years of age. Fifty-five percent (55%) of the patients were men and 45% were women. Prior chemotherapy for AML, baseline demographic and diseases characteristics are shown in table 7, 8 and 9.

Table 7 - Baseline demographic (studies 0903B1-201-US/CA, 0903B1-202-EU, 0903B1-203-US/EU)

Characteristic	Number of Patients (n = 277)
Age, years	
Mean (SD)	58.2 (14.1)
Median	61.0
Min – Max	20.0 - 87.0
Age ≥ 60, n (%)	157 (57)
Age < 60, n (%)	120 (43)
Sex, n (%)	
Female	126 (45)
Male	151 (55)
Ethnic origin, n (%)	
White	264 (95)
Black	6 (2)
Asian	2 (< 1)
Other	5 (2)

Abbreviations: Max = maximum; Min = minimum; SD = standard deviation.

Table 8 – Prior chemotherapy and duration of first remission (studies 0903B1-201-US/CA, 0903B1-202-EU, 0903B1-203-US/EU)

Statistic	Number of patients (n = 277)
Second induction, n/N (%)	38/268 (14)
Postremission therapy, [a] n (%)	248/266 (93)
Cycles of post-remission therapy	
n	266
Mean (SD)	2.2 (1.5)
Median	2.0
Min – Max	0 -11
HiDAC, n (%)	172/272 (63)
Duration of first remission, months	
n	277
Mean (SD)	14.7 (14.1)
Median	10.6
Min – Max	2-117
Duration of first remission,	
Number of patients in each category (%)	
<6 months	39 (14)
6 to 12 months	126 (46)
≥12 months	112 (40)

[a] Determination was based on the medications collected on the prior chemotherapy case report form. Any chemotherapy medication started at ≥20 days after first CR was considered postremission therapy.
Abbreviations: CR = complete remission; HiDAC = high-dose cytarabine; Max = maximum; Min = minimum; SD = standard deviation

Table 9 – Prestudy cytogenetics for patients in studies 0903B1-201-US/CA, 0903B1-202-EU, 0903B1-203-US/EU

Prognonsis[a] (n = 277)	Number of Patients at Initial Presentation (%)	Number of Patients at First Relapse (%)
Poor	56 (20)	63 (23)
Intermediate	136 (49)	112 (40)
Favourable	8 (3)	6 (2)

[a] Cytogenetics were not available for all patients at either initial diagnosis or first relapse. Thus, percentages may not sum to 100%.

Outcomes and estimation

Remission rates

Complete response rates were 17%, 14% and 8% for studies 0903B1-201-US/CA, 0903B1-202-EU, 0903B1-203-US/EU respectively, with an overall average of 13%. Results based on the protocol-defined and IWG-defined (*) criteria are presented in the tables 10 and 11.

Table 10: Protocol-defined remission rates (studies 0903B1-201-US/CA, 0903B1-202-EU, 0903B1-203-US/EU)

	Number of Patients (%) and 95% Confidence Interval			
Remission Category	Study 201 (n=84)	Study 202 (n=95)	Study 203 (n=98)	Pooled Studies 201/202/203 (n=277)
CR (%)	14 (17)	13 (14)	8 (8)	35 (13)
95% CI[a]	9, 26	7, 22	4, 15	9, 17
CRp (%)	13 (15)	11 (12)	12 (12)	36 (13)
95% CI[a]	9, 25	6, 20	16, 20	9, 18
OR (CR + CRp) (%)	27 (32)	24 (25)	20 (20)	71 (26)
95% CI[a]	22, 43	17, 35	13, 30	21, 31

a. Method of Clopper and Pearson.
Abbreviations: CR = complete remission; CRp = complete remission with incomplete platelet recovery; OR = overall remission.

Table 11: IWG-defined remission rates (studies 0903B1-201-US/CA, 0903B1-202-EU, 0903B1-203-US/EU)

	Number of Patients (%) and 95% Confidence Interval			
Remission Category	Study 201 (n=84)	Study 202 (n=95)	Study 203 (n=98)	Pooled Studies 201/202/203 (n=277)
CR* (%)	18 (21)	15 (16)	9 (9)	42 (15)
95% CI[a]	13, 32	9, 25	4, 17	11, 20
CRp* (%)	15 (18)	17 (18)	22 (22)	54 (19)
95% CI[a]	10, 28	11, 27	15, 32	15, 25
OR* (CR* + CRp*) (%)	33 (39)	32 (34)	31 (32)	96 (35)
95% CI[a]	29, 51	24, 44	23, 42	29, 41

a. Method of Clopper and Pearson.
Abbreviations: IWG = International Working Group; CR* = complete remission; CRp* = complete remission with incomplete platelet recovery; OR* = overall remission.

Relapse-Free Survival (RFS)

The median RFS was 6.4 months for patients with CR and 4.5 months for patients with CRp. The corresponding figures were 7.5 and 4.4 with the IWG criteria.

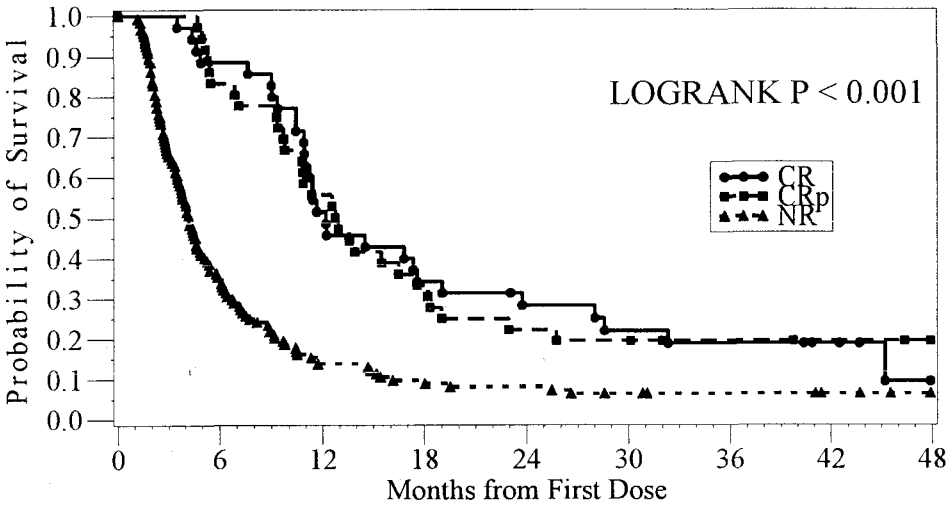
Overall Survival

The median survival was 4.8 months. The early death rate (deaths from first dose to 28 days after the last dose) was 16% for all patients. The probability of survival beyond 12 and 24 months was 0.22 and 0.12, respectively.

Survival by remission category

The median OS, analyzed using protocol-defined criteria, was 12.2 months for patients with CR, 12.8 months for patients with CRp, and 4.2 months for patients not responding to treatment (12.9, 9.6 and 3.0, respectively according to IWG criteria). Overall survival was significantly different between CR and patients with no response and between CRp and patients with no response ($p<0.001$). There was no significant difference in survival between patients with CR and CRp ($p=0.804$). See figure 1.

Figure 1: Survival for CR, CRp, and NR Patients



Time to Clearance of Leukaemic Blasts

Gemtuzumab ozogamicin produced rapid clearance of aspirate bone marrow blast cells. A total of 147 (53%) patients achieved blast clearance according to protocol-defined criteria. Of the patients who had blast clearance, 53% cleared blasts after the first dose, 46% cleared blasts after the second dose, and 1% cleared blasts after the third dose. Twenty-one (60%) of the CR patients and 16 (44%) of the CRp patients had blast cell clearance after the first dose of gemtuzumab ozogamicin.

Absolute Neutrophil Count Recovery

The median times for ANC recovery to 0.5 x 10^9/L for the CR and CRp patients were 40.0 and 43.0 days, respectively (CR vs. CRp, p = 0.249) and were significantly shorter than for NR patients (51 days; CR vs. NR, p=0.0001; CRp vs. NR, p=0.0023).

Platelet Recovery

Time from first dose of gemtuzumab ozogamicin for patients to reach a platelet count of 25 x 10^9/L was evaluated. The median recovery of platelet counts to reach 25 x 10^9/L was 36.0 and 51.0 days for CR and CRp patients, respectively. These times were significantly shorter than those for NR patients (175 days, p=0.0001). One CRp patient did not achieve a platelet recovery to 25 x 10^9/L.

Other antileukaemic therapy and HSCT after treatment with gemtuzumab ozogamicin

Overall, 48.7% of patients received no other therapy after gemtuzumab ozogamicin. Median RFS was longer for CR patients who received HSCT than for patients who received other chemotherapy or no further therapy after treatment with gemtuzumab ozogamicin (p<0.001). A summary tabulation of patients with RFS by post-remission therapy is presented below.

Table 12: Protocol-defined RFS in studies 0903B1-201-US/CA, 0903B1-202-EU, 0903B1-203-US/EU by post-remission therapy

	Median and 95% Confidence Intervals					
	CR		CRp		OR	
Postremission Therapy	Median (months)	95% CI	Median (months)	95% CI	Median (months)	95% CI
Allogeneic HSCT	7.3	(1.8,-)	--[a]	--[a]	--[a]	--[a]
Autologous HSCT	8.9	(6.7, 10.5)	13.2	(2.9,-)	9.0	(5.4,22.4)
Other chemotherapy	5.0	(2.0,7.7)	5.1	(3.0,7.1)	5.1	(3.0,7.1)
No other therapy	3.8	(1.8,6.6)	2.3	(1.8,3.0)	2.5	(2.1,4.0)

A median was not reached. Abbreviations: CR = complete remission, CRp = complete remission with incomplete platelet recovery, HSCT = hematopoietic stem cell transplantation; OR = overall remission; CI = confidence interval.

A significant difference in overall survival was observed among patients in remission who received therapy after treatment with gemtuzumab ozogamicin. While the median survival for all patients was