12.2 months for CR and 12.8 months for CRp patients, the median survival for patients who received HSCT (either allogeneic or autologous) after gemtuzumab ozogamicin-induced remission was 18.1 months (17.1 month in IGW analysis). The median survival for patients who received post-remission chemotherapy was 10.7 months compared to 11.0 months for patients who did not have any post-remission therapy (10.0 and 10.3, respectively for IGW analysis). Post-HSCT survival was similar for CR, CRp, and NR patients (p=0.070).

Patients intended to undergo HSCT

In the pivotal phase II, 16% (44/277) of patients underwent post-gemtuzumab ozogamicin HSCT, 38% (16/42) patients with CR*, 24% (13/54) patients with CRp* and 8% (15/181) with NR*. The median post-HSCT survival for all patients with remission was 11.8 months compared with 6.0 months for NR* patients.

Duration of first remission less than 12 months

Table 13: Rates of remission in studies 0903B1-201-US/CA, 0903B1-202-EU, 0903B1-203-US/EU by Duration of First Remission

	Number (%) of remission patients/total number of patients					
	CR*		CRp*		OR*	
Duration of First Remission	**n/Total[a] (%)**	**95% CI**	**n/Total[a] (%)**	**95% CI**	**n/Total[a] (%)[b]**	**95% CI**
< 6 months	2/39 (5)	(1, 17)	6/39 (15)	(6, 31)	8/39 (21)	(9, 36)
≥ 6 to < 12 months	17/126 (13)	(8, 21)	24/126 (19)	(13, 27)	41/126 (33)	(24, 41)
≥ 12 to < 24 months	17/79 (22)	(13,32)	21/79 (27)	(17, 38)	38/79 (48)	(37, 60)
≥ 24 months	6/33 (18)	(7, 35)	3/33 (9)	(2, 24)	9/33 (27)	(13, 46)

Abbreviations: CR* = complete remission; CRp* = complete remission with incomplete platelet recovery; OR* = overall remission; CI = confidence interval.

a. Total = all patients who were classified in the specified remission duration subgroup.

b. Percentages do not add up because of rounding.

Data from statistical report a05_a302 (02 May 2005).

Patients over the age of 60 years with duration of first remission less than 12 months

Data from three clinical trials conducted by the United Kingdom MRC (AML-11, AML-12 and AML-14), enrolled a total of 1068 patients across the trials and encompassed patients whose age was over 60 years. The majority of the patients had a first relapse duration of less than 12 months. These patients, all of whom were in first relapse, were studied for outcomes after re-induction treatment. Patients in this age group with a first relapse experienced CR rates in the order of 11% to 14% (n=706), see table 14. Of 706 patients, 389 patients received re-treatment following relapse, and second CR rates ranged from 15% to 19%.

Table 14: Re-treatment outcomes following first relapse in patients older than 60 years: AML11, AML12 and AML14 studies

Duration of remission	Percentage (n/N) of patients who achieved CR[a]
<6 months	11% (35/324)
<9 months	11% (60/524)
<12 months	14% (100/706)
p-value for trend	0.001

a. CR is based primarily on the clearance of leukemic blast cells from the bone marrow, therefore, the "CR" groups presented in this table includes patients with both CR and CRp.

- Discussion on clinical efficacy

A total of 277 patients were evaluated for clinical efficacy after the pooling of studies 0903B1-201-US/CA, 0903B1-202-EU, 0903B1-203-US/EU. The median age of patients was 61 years old. The duration of first remission during previous treatment was <6 months remission in 14% of patients, 6-12 months for 46% of patients and ≥ 12 months for 40% of patients in the trial. In general, patients with duration of a first CR less than 12 months have a poor outcome to second-line re-induction

therapy. Approximately, 70% of the patients received high-dose Ara-C as part of prior first-line therapy. In the FAB classification, the M2 subtype was the most common (26%), 21% had M1, 20% had M4 and 11% had M5 at relapse. Cytogenetically, 40% of patients had an intermediate prognosis at first relapse, 23 % had a poor prognosis pattern and 2% had favourable prognosis. Multi-drug resistance (MDR) status was assessed. Most patients, regardless of remission category, demonstrated pre-treatment increased MDR pattern.

Efficacy data demonstrated that the primary goal to reach a response rate not inferior to published results from studies with other agents is hardly reached if the classic CR definition (defined in the protocol and recommended by the CHMP) is used: only 13% of patients reached CR. Only when the group of patients with CRp was included, the ORR rate reached 26% (35% according to the IWG response classification), which is comparable to data in the literature for true CR (from 20-70% in the series reviewed by the Applicant). The response rate did not vary with age, cytogenetic classification or gender, but did vary with duration of first (previous) remission. A total of 53% achieved blast clearance (not identical to CR) according to protocol-defined criteria. Of the patients who had blast clearance, about half cleared blasts after the first dose, and half after the second dose. 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. Median recovery time of platelet counts to 25 x 10^9/l for CR and CRp patients was 36.0 and 51.0 days, respectively. Thus both results indicate that gemtuzumab ozogamicin treatment may belong to the so-called intensive therapy, since severe myelosuppression is observed.

In terms of consolidation therapy, 25 (35.2%) of the 71 OR patients received either allogeneic or autologous HSCT while they were in remission (11 CR patients and 14 CRp patients). A total of 96 (34.7%) patients received only other chemotherapy that was not part of a preparative regimen for HSCT. A significantly greater proportion of NR patients than OR patients received additional chemotherapy only ($p<0.001$). Overall, 48.7% of patients received no other therapy after gemtuzumab ozogamicin, with no difference in frequency between OR and NR patients.

Median relapse-free survival (RFS), the secondary efficacy parameter, was 6.4 months for CR and 4.5 months for CRp patients (half the patients received consolidation therapy with autologous or allogeneous stem cell transplantation or chemotherapy alone). For those 35 patients who received no consolidation, the RFS was 2.5 months for the CR+CRp group.

The median overall survival (OS) was 4.8 months for all patients. The early death rate (death within 28 days) was 16%. Median survival for responders (CR+CRp) was 12.5 months, in part a reflection of consolidation therapy, since it was 18.1 months for those receiving consolidation *versus* 11.0 months for those receiving no consolidation. The difference from the much shorter RFS in this last group (2.5 months) indicates that many of these patients received and tolerated further chemotherapy after relapse.

Conclusions on the influence of age, sex, previous response, cytogenetics or biomarkers (data not shown) on survival is not possible to evaluate, since only 35 patients received no further therapy and the rest received various types of intensive consolidation therapy.

Overall, the three small phase II studies demonstrated that gemtuzumab ozogamicin is a potent myelosuppressive agent which has a limited selectivity for leukaemic cells since the CR rate was 13% (26% CR+CRp) in first relapse AML patients. The RFS was 6.4 months for CR patients, including the consolidation therapy, but only 3.8 months for the CR patients (2.5 months for the overall remission group) receiving no consolidation therapy.

Consultation of the oncology scientific advisory group

Following the CHMP request, an oncology Scientific Advisory Group (SAG) meeting was convened on 30 November 2006 to provide advice on the list of questions raised by the Committee, in the context of the restricted claimed indication i.e, *Mylotarg is indicated for induction treatment of CD33-positive acute myeloid leukaemia patients in first relapse who are not considered candidates for other cytotoxic chemotherapy.* The following questions were raised and discussed:

- One of the limitations of this application was that the modest proportion of CR and CRp and the lack of reliable data on duration of remission. Furthermore, with reference to CPMP Scientific Advice CPMP/727/99, CR and CRp were considered insufficient to establish therapeutic efficacy in the proposed therapeutic indication. In the proposed therapeutic

indication, progression-free survival and overall survival would have been considered the relevant primary endpoints. What type of acute myeloid leukaemia patients in first relapse would not be considered candidates for other cytotoxic chemotherapy? What are the treatment options available for these patients?

AML patients with a first relapse are generally treated with chemotherapeutic regimens, including high-dose induction regimens in younger patients and allogeneic HSCT. A number of cytotoxic agents and combination regimens have been used for the salvage chemotherapy, and CR rates from 20 - 70 % have been described with remission duration of typically 4 to 6 months, results which vary depending on prognostic factors such as duration of the first remission, cytogenetics and age. However, the SAG/CHMP considered that in the case where patients are not eligible for high-dose induction-type regimens, this would not mean that they are ineligible for any other cytotoxic chemotherapy. Indeed, a number of treatment options are available, including for example low-dose cytarabine or hydroxyurea but more in a palliative setting. Thus, it is difficult to define and discriminate a population of patients with a first relapse who would not be considered candidates for other cytotoxic chemotherapy.

- Based on the proportion of CR and CRp, and other available clinical efficacy results, can it be concluded that treatment with gemtuzumab ozogamicin is associated with a clinical benefit for the patients in the claimed indication? Is the study population representative of the target population in the claimed indication?

The oncology SAG considered that the claimed indication refers to a theoretical situation where no other therapeutic option is available. For this indication, the clinical studies presented do not provide sufficient data to estimate the proportion of responders or clinical benefit. The study population is not representative of the target population for the claimed indication since patients were eligible for other cytotoxic chemotherapy and some of the patients underwent high-dose chemotherapy and allogeneic HSCT afterwards.
Concerning a claimed indication for acute myeloid leukaemia patients with a first relapse, the activity of gemtuzumab ozogamicin as compared to available treatment options is unclear. In terms of relevant clinical endpoints, there is no comparative data available. In addition, activity of gemtuzumab ozogamicin compared unfavourably with a number of cytotoxic agents and combination regimens that have a proportion of CR ranging from 20% to 70%, as described in the literature. Therefore, the SAG is of the opinion that the study population is not representative of the target population for the claimed indication.

- Would a randomized controlled trial with single-agent gemtuzumab ozogamicin in the claimed indication be feasible in European Union? What would be the comparator?

The SAG considered that the claimed indication refers to a theoretical situation where no other option is available (indeed some of the patients were afterwards treated with high-dose chemotherapy and HSCT). This population is difficult to identify and no studies are considered feasible. Concerning patients that are not eligible for chemotherapeutic regimens, theoretically one could envisage a randomized trial against the investigator's choice. There should be considerable interest for such a trial to achieve sufficient enrolment and make the trial feasible. In light of the modest activity observed and the significant toxicity, it is doubtful that further investigation of single-agent treatment with gemtuzumab ozogamicin (or other existing agent) is deemed of sufficient interest.

- From a clinical perspective, what are the most important benefits, toxicity and risks associated with treatment with gemtuzumab ozogamicin? What is the strength of evidence and what are the remaining uncertainties?

The SAG considered that the anti-leukemic activity of gemtuzumab ozogamicin has been established but it is difficult to quantify the clinical benefits in the context of other available treatment options. It is not possible to assess the treatment effect in terms of relevant clinical endpoints such as relapse-free survival and overall survival since the study population is not deemed representative of the target population for the claimed indication. Whether the potential benefits of gemtuzumab ozogamicin compare favourably with those of alternative treatment options is yet unknown. Concerning toxicity, gemtuzumab ozogamicin does not have an unusual profile compared to other AML induction

regimens, which typically show severe and long-standing myelosuppression. However, differences for gemtuzumab ozogamicin include infusion-related side effects, liver toxicity and VOD, especially when combined with HSCT.

During an oral explanation to the CHMP, the applicant argued that it was not feasible to conduct further studies in the sought indication against either active comparator, placebo, or supportive care due to the current state of knowledge, the small target population, and medical ethics. On that basis, the applicant requested that Mylotarg be considered for a marketing authorization under exceptional circumstances. In addition, the applicant provided an overview of ongoing and planned clinical trials.

The CHMP acknowledged the lack of a single standard treatment for AML in first relapse, and the practical difficulties in conducting a randomised controlled trials in this setting. However, the CHMP considered that a randomised trial against e.g. the investigator's choice could be envisaged. In addition, the CHMP considered that the planned and ongoing randomised phase III trials to assess the efficacy and safety of gemtuzumab ozogamicin in combination and used as a first-line anti-leukaemic agent, would not provide any relevant information on the efficacy of gemtuzumab ozogamicin in the claimed indication.

Clinical safety

- Patient exposure

The assessment of the safety profile of gemtuzumab ozogamicin was based on three dose-escalation phase I studies and three pivotal phase II studies. A total of 495 patients with AML were exposed to gemtuzumab ozogamicin in the clinical studies, including 29 children; 442 additional patients were exposed to gemtuzumab ozogamicin in a single arm ongoing prospective observational study.

- Adverse events

In the pivotal studies, the most frequent abnormalities were hematologic abnormalities, including platelets (99%), total absolute neutrophils (98%), white blood cells (96%), and lymphocytes (94%) abnormalities. The most frequent (reported in ≥30% of the patient) non-hematologic adverse drug reactions (ADR) were fever (74%), chills (60%), nausea (55%), and vomiting (47%). Non-hematologic ADR occurring in ≥10% of the patient are shown in table 15. Severe (grade 3 or 4) fever was reported in 12% of patients. All patients had grade 3 or 4 laboratory abnormalities. After a second course of gemtuzumab ozogamicin, the most frequent non-hematologic grade 3 or 4 ARs were stomatitis (15%), pneumonia (15%), neutropenic fever (15%), hypertension (10%), hypotension (10%), respiratory distress syndrome (10%), and respiratory failure (10%).

Table 15: Non- hematologic ADRs occurring in ≥10% of the patient population during part 1 of studies 0903B1-201-US/CA, 0903B1-202-EU, 0903B1-203-US/EU.

Body System Adverse Event	Number (%) of Patients (n = 277)
Body as a Whole	
Abdominal pain	42 (15)
Asthenia	74 (27)
Chills	167 (60)
Fever	206 (74)
Headache	60 (22)
Neutropenic fever	42 (15)
Sepsis	31 (11)
Cardiovascular System	
Hypotension	37 (13)
Digestive System	
Anorexia	46 (17)
Diarrhea	45 (16)
Liver function tests abnormal	59 (21)
Nausea	153 (55)
Stomatitis	42 (15)
Vomiting	129 (47)
Hemic and Lymphatic System	
Petechiae	34 (12)
Metabolic And Nutritional	

Body System Adverse Event	Number (%) of Patients (n = 277)
Bilirubinemia	28 (10)
Lactate dehydrogenase increased	34 (12)
Respiratory System	
Epistaxis	47 (17)
Skin and Appendages	
Herpes simplex	28 (10)

Infusion related adverse reaction occurred on the same day of infusion. Symptoms generally started at the end of the 2-hour i.v. infusion and resolved after 2 to 4 hours post-infusion with supportive therapy of paracetamol, diphenhydramine, and intravenous fluids. The most frequent severe non-hematologic infusion-related adverse reactions (ARs) (National Cancer Institute [NCI] grade 3 or 4) were chills (8%), fever (6%), and hypotension (4%).

Three serious hypersensitivity reactions were reported in patients included in the pivotal studies. Myelosuppression was an expected and frequent complication of gemtuzumab ozogamicin. During the treatment phase, 267 (98%) and 272 (99%) patients had grade 3 or 4 neutropenia and/or thrombocytopenia, respectively. Patients with OR recovered to an ANC of 0.5 x 10^9/L by a median of 43.0 days and platelet counts recovered to 25 x 10^9/L by a median of 33.5 days after the first dose of gemtuzumab ozogamicin. Grade 3 or 4 anemia was reported in 143 (52%) patients. During the treatment phase, 36 (13%) patients experienced grade 3 or 4 bleeding, including epistaxis (3%), cerebral hemorrhage (2%), intracranial hemorrhage (1%), hematuria (1%), melena (1%), and petechiae (1%).

In the pivotal studies, 106 (39%) patients experienced grade 3 or 4 abnormalities in liver function tests, including hyperbilirubinemia (29%), abnormalities in levels of alanine aminotransferase (9%) and aspartate aminotransferase (18%), concurrent elevations of aminotransferases and bilirubin (9%). Most of the observed laboratory changes were transient, reversible, and required no medical intervention. Ascites was observed in 8 patients and were considered mild to moderate in severity.

A total of 16 episodes of veno-occlusive disease VOD (in 15 patients) were identified (16/299, 5%). The incidence of VOD in patients treated with gemtuzumab ozogamicin who had no prior or subsequent HSCT was 1%. The risk of developing VOD was 19% for patients with a history of HSCT prior to gemtuzumab ozogamicin administration (see table 16). In patients who received HSCT after gemtuzumab ozogamicin administration, the risk of developing VOD was 16%.

Table 16: Incidence of VOD for patients receiving gemtuzumab ozogamicin with or without HSCT in studies 0903B1-201-US/CA, 0903B1-202-EU, 0903B1-203-US/EU.

Patient Category	Number of Patients in Classification	Number of Patients With VOD	Incidence of VOD (in patients)	Number of Courses of GO	Number of Episodes of VOD	Incidence of VOD (episodes per courses)
GO Total	277	15	5%	299 [a]	16	5%
GO Only	200	2	1%	214 [b]	2	1%
HSCT with GO (total)	77	13	17%	85 [c]	14	16%
HSCT before GO	27 [d]	5	19%	29	5	17%
HSCT after GO	50 [d]	8	16%	56	9 [e]	16%

a. 20 patients received 22 additional courses of gemtuzumab ozogamicin.
b. 11 patients who received gemtuzumab ozogamicin and never had HSCT also received a second course of gemtuzumab ozogamicin and 1 received 3 additional courses of gemtuzumab ozogamicin.
c. 8 patients who received gemtuzumab ozogamicin and had HSCT received 2 courses of gemtuzumab ozogamicin.
d. Patients were categorized as having "HSCT before GO" or "HSCT after GO" based upon the relative timing of the first HSCT and the first course of gemtuzumab ozogamicin. Thus, patients who had HSCT both before and after gemtuzumab ozogamicin were included in "HSCT before GO" and not in "HSCT after GO." Patients who received courses of gemtuzumab ozogamicin before and after a single HSCT were included in "HSCT after GO" and not in "HSCT before GO."
e. 1 patient had 2 episodes of VOD. This patient received gemtuzumab ozogamicin, had HSCT, and developed VOD. A second course of gemtuzumab ozogamicin was administered, after which the patient developed fatal VOD. This patient and both of these episodes of VOD were included in the "HSCT after GO" group based on the timing of the first course of gemtuzumab ozogamicin relative to HSCT.

Abbreviations: GO = gemtuzumab ozogamicin; HSCT = hematopoietic stem cell transplantation; VOD = veno-occlusive disease

During the pivotal trials, severe grade of ADRs (NCI grade 3 or 4) was reported for tumor lysis syndrome (TLS)(4 patients, 1%), mucositis (9 patients, 3%), nausea (24 patients, 9%), vomiting (11 patients, 4%), and diarrhea (2 patients, <1%). Grade 3 or 4 infections were reported for 87 patients (31%). The most frequent infections were sepsis (23 patients, 8%), pneumonia (13 patients, 5%), shock and infection (4 patients each, 1%), stomatitis and herpes simplex (3 patients each, 1%). Patients also reported ADR associated with severe renal impairments (10 patients, 4%), including face edema (3 patients, 1%), acute kidney failure and kidney failure (2 patients each, <1%), generalized edema and kidney pain (1 patient each, <1%). Patients experienced cardiovascular ADRs (83 patients, 30%), the most frequent (incidence ≥5%) of which were hypotension (13%), hypertension (6%) and tachycardia (6%). Severe cardiovascular ADRs included hypotension (5%), hypertension (3%), and chest pain, cardiac tamponade, pericarditis, tachycardia, and tachycardia sinus (1 patient each, <1%). Skin ADRs included pruritus (18 patients, 6%) and skin rash (51 patients, 18%). Severe pruritus and skin rash was reported for 1 (<1%) and 4 (1%) patients, respectively. Cutaneous herpes simplex was reported in 59 patients (21%). No patient in the pivotal trials experienced drug-related alopecia. ADRs associated with severe neurologic impairment (grade 3 or 4) were reported (10 patients, 4%) , including 3 reports of confusion (1%), 2 reports of eye disorder (<1%), and 1 report each of agitation, CNS depression, convulsion, facial paralysis, hypertonia, paresis, somnolence, stupor, and tremor (<1% for each).

Adverse events after post-remission therapy

Fifty-two patients received HSCT after administration of gemtuzumab ozogamicin. Among these patients, 27 patients (52%) reported grade 3 or 4 ADRs that occurred after HSCT. The most frequent ADRs were VOD (10%), immune system disorder (8%), sepsis (8%), bilirubinemia (6%), stomatitis (6%) and kidney failure (6%).
Among the 109 patients who received additional antileukaemic therapy after gemtuzumab ozogamicin, 13 patients (11%) had grade 3 or 4 adverse events related to gemtuzumab ozogamicin, including thrombocytopenia (3%), leukopenia (3%), sepsis (2%), and VOD (2%).

- Serious adverse event/deaths/other significant events

Disease progression was the most frequent cause of early mortality in the phase I. In study 0903A1-101-US, 6 of the 7 deaths within 30 days after gemtuzumab ozogamicin were due to disease progression and 1 was due to infection. In the pediatric study (0903A1-102-US), 3 deaths within 28 days after gemtuzumab ozogamicin were due to disease progression. In study 0903A1-103-JP, 14 of

the 16 deaths in the dose-escalation phase of the study (phase 1) were due to disease progression, 1 was due to pulmonary hemorrhage (occurring on the same day as gemtuzumab ozogamicin administration) and 1 cause of death was unknown. In the pivotal studies, 44 of the 277 patients (16%) died within 28 days of receiving the last dose in the first course of gemtuzumab ozogamicin treatment. Disease progression was the primary cause of death in 13 cases. In addition, 13 patients died of infection (including pneumonia, sepsis, septic shock, and other infections), 8 of hemorrhage, 4 of multiorgan failure, 3 of respiratory failure, 1 of VOD, and 1 of anaphylactic reaction to amphotericin B. One cause of death was not recorded. In 15 patients that developed VOD, 10 patients had fatal VOD or ongoing VOD at the time of death.

- Laboratory findings

A total of 126 patients (46%) had a kidney laboratory values of potential clinical importance (PCI); most of these changes were related to potassium (34%) or sodium levels (17%); 16 patients (6%) had a creatinine level >2 x upper normal limit (UNL), and 3 patients (2%) had elevated blood urea nitrogen (BNU) levels.

Table 17: Patients with renal laboratory tests in studies 0903B1-201-US/CA, 0903B1-202-EU, 0903B1-203-US/EU.

Category **Test Unit**	**Number with PCI/number tested (%)**
Any renal laboratory test	126/276 (46)
Blood Chemistry	
Blood urea nitogren (mmol/l)	
All (>25)	3/140 (2)
High (>25)	3/140 (2)
Creatinine (mcmol/l)	
All (>2x ULN)	16/276 (6)
Potassium (mmol/l)	
All	93/276 (34)
High (>5.5)	6/276 (2)
Low (<3.2)	88/276 (32)
Sodium (mmol/l)	
All	47/276 (17)
High (>150)	4/276 (1)
Low (<130)	45/276 (16)

Abbreviation: PCI = potential clinical importance

- Safety in special populations

Paediatric Population: Most of the deaths that occurred during the paediatric study 0903A1-102-US were attributable to disease progression or to complications associated with HSCT. All patients exhibited myelosuppression. Other toxicities included grade 3 or 4 fever (24%), hyperbilirubinemia (7%), mucositis (3%) and sepsis (17%). 5 (17%) of 29 patients developed VOD; 4 of these patients developed VOD after receiving HSCT.

Elderly: Detailed analyses of differences between patients ≥60 years of age and patients <60 years of age suggest similarity with respect to the incidence of most frequent severe ADRs (data not shown).

Gender: Grade 3 or 4 ADRs for female and male patients were similar (data not shown).

- Safety related to drug-drug interactions and other interactions

Clinical drug-drug interaction studies were not conducted with gemtuzumab ozogamicin.

- Discontinuation due to adverse events

Twenty-six (9%) patients discontinued treatment due to adverse events during part 1 of the pivotal studies; 15 (58%) of these patients discontinued treatment due to drug-related adverse events.

- Post marketing experience

From 01 May 2000 to 28 February 2005, 15 465 patients were exposed to gemtuzumab ozogamicin. There were 895 reports of serious adverse events (SAEs); 466 of these cases reported more than 1 event. The system organ classes (SOCs) with the greatest number of serious events were blood and lymphatic system disorders (n=318), general disorders and administration site conditions (n=288) and

hepatobiliary disorders (n=221). The most frequently reported SAEs were pyrexia (n = 103), sepsis (n=82), liver disorder (n=82), and AML (n=77). A total of 363 deaths have been reported to date in post-marketing up to 15 March 2005. Among the death reports, the SOCs with the most frequently reported primary events were hepatobiliary (n=81), neoplasms (n=58), and infections and infestations (n=56). The most frequently reported causes of death were AML (n=54), liver disorder (n=47), sepsis (n=26), and multiorgan failure (n=21).

- Discussion on clinical safety

The cumulative experience with gemtuzumab ozogamicin suggests it is rather well tolerated in patients of all ages receiving treatment for AML in first relapse. The safety profile did not differ between patients <60 years and patients ≥60 years in the pivotal trials.

The main safety issues consisted of severe myelosuppression, hepatotoxicity including veno-occlusive disease (VOD) and infusion related events.

Myelosuppression is an expected and frequent complication of both conventional chemotherapy and targeted therapy with gemtuzumab ozogamicin. Differentiated hematopoietic precursor cells that are $CD33^+$ are targeted by gemtuzumab ozogamicin and, consequently, this leads to myelosuppression. Severe myelosuppression occured when gemtuzumab ozogamicin was used at the recommended doses: 98% of patients in the pivotal trials experienced grade 3-4 suppression of neutrophil and platelet counts of at least 5-6 weeks duration. Despite platelet transfusions, 13% of patients had grade 3-4 bleeding and 4% had cerebral bleeding, which proved fatal in 8 patients. The neutropenia was accompanied by infections (grade 3-4 in 31% patients), which is a relatively rare occurrence for AML treatment. Deaths due to infection or bleeding have been reported during the period of severe myelosuppression. Therefore, careful haematologic monitoring is required and systemic infections must be treated.
Hepatotoxicity, including severe veno-occlusive disease (VOD), has been reported in association with the use of gemtuzumab ozogamicin as a single agent, as part of combination chemotherapy regimen, and in patients without a history of liver disease or haematopoietic stem cell transplant (HSCT). A multivariate analysis demonstrated that HSCT, whether performed before or after gemtuzumab ozogamicin, was a significant risk factor for VOD. It has been shown that patients who received HSCT before gemtuzumab ozogamicin (19%), and patients who received HSCT following gemtuzumab ozogamicin (16%), were at higher risk of developing VOD than patients who had not been transplanted. Death from liver failure from VOD was reported in patients who received gemtuzumab ozogamicin. Grade 3 or 4 renal events were reported for 10 patients (4%), including face oedema (1%), acute kidney failure (1%), kidney failure (1%), generalized oedema, abnormal lab test and kidney pain (all <1%). Grade 3 or 4 tumor lysis syndrome (TLS) was reported for 4 patients (1%) involved in the pivotal studies. TLS may be a consequence of leukaemia treatment with any chemotherapeutic agent, including gemtuzumab ozogamicin. Renal failure secondary to TLS has been reported in association with the use of gemtuzumab ozogamicin. Electrolytes, tests of hepatic and renal function, complete blood counts and platelet counts must be monitored during gemtuzumab ozogamicin therapy.
Gemtuzumab ozogamicin administration can result in severe hypersensitivity reactions (3 SAEs related to hypersensitivity were reported during the pivotal studies), including anaphylaxis, and other infusion-related reactions, which may include severe pulmonary events. Most cases of hypersensitivity reactions and pulmonary events have not been fatal. In many instances, infusion-related symptoms occurred during the infusion or within 24 hours of administration of gemtuzumab ozogamicin.
Severe pulmonary events leading to death have been reported infrequently with the use of gemtuzumab ozogamicin in the postmarketing experience. Signs, symptoms and clinical findings include dyspnoea, pulmonary infiltrates, pleural effusions, non-cardiogenic pulmonary edema, pulmonary insufficiency and hypoxia, and acute respiratory distress syndrome. These events occur as sequelae of infusion reactions and patients with white blood cell counts ≥30,000/µL may be at an increased risk.
Cardiovascular events (grade 3 or 4) were reported in 20% of patients. Early mortality (death within 28 days) affected 16% of patients. The majority of deaths in follow-up (208 patients) were due to disease progression.

No clinical drug-drug interaction studies were conducted with gemtuzumab ozogamicin. The potential for interaction of gemtuzumab ozogamicin with drugs affected by cytochrome P450 enzymes cannot be ruled out. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take gemtuzumab ozogamicin. As gemtuzumab ozogamicin contains 2-mmol (or 46 mg) sodium per dose, patients on a controlled sodium diet need to take this into consideration.
Two patients in a Phase I study developed antibody titers against the calicheamicin/calicheamicin-linker portion of gemtuzumab ozogamicin after administration of three doses. One patient experienced transient fever, hypotension and dyspnoea; the other patient had no clinical symptoms. Patients treated with gemtuzumab ozogamicin did not experienced drug-related alopecia.
Gemtuzumab ozogamicin can produce a post-infusion symptom complex of fever and chills (grade 3-4 in 35% patients), and less commonly, hypotension and dyspnoea, which may occur during the first 24 hours after administration. The incidence fell from 31% following the first dose to 10% after the second dose.
No cases of overdose with gemtuzumab ozogamicin were reported in clinical experience. Single doses higher than 9 mg/m^2 in adults were not tested. No studies on the effects on the ability to drive and use machines were performed.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan. The CHMP, having considered the data submitted in the application was of the opinion that it was not appropriate to consider risk minimisation activities at this time.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of this product was considered to be acceptable. Physicochemical and biological aspects relevant to the overall clinical performance of the product were investigated and were found to be controlled in a satisfactory way. The evaluation confirmed that only the product obtained using a source material from human origin from an authorised plasma source that is covered by a centrally approved Plasma Master File would be acceptable for release on the EU market. Data on viral/TSE safety were reassuring and it is considered that the risk of virus transmission to patients receiving Mylotarg is remote. Nevertheless, the purification process would have to be further improved to increase its viral removal capacity.

Non-clinical pharmacology and toxicology

Gemtuzumab ozogamicin is a monoclonal antibody, cytotoxic to the CD33 positive HL-60 human leukaemia cell line. The binding of the anti-CD33 antibody portion of gemtuzumab ozogamicin with the CD33 antigen results in the formation of a complex that is internalized. Upon internalization, the calicheamicin derivative is released inside the liposomes of the myeloid cell, resulting in DNA double strand breaks and cell death. In preclinical animal studies, gemtuzumab ozogamicin has demonstrated anti-tumour effects in the HL-60 human pro-myelocytic leukaemia engraft tumour in mice.
Single and repeat dose toxicity studies were conducted in the rat and cynomolgus monkey. The toxicity of gemtuzumab ozogamicin was dominated by cytotoxic actions on dividing cells after high doses, and by renal tubular and hepatic damage. No studies were conducted to assess the carcinogenic potential of gemtuzumab ozogamicin. Gemtuzumab ozogamicin induced clastogenic effects in mice *in vivo* micronucleus test. This positive result is consistent with the ability of calicheamicin to cause double-stranded breaks in DNA.
Gemtuzumab ozogamicin adversely affected fertility in male rats (decreased fertility rates, reduced sperm counts and sperm motility, 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 was associated with maternal toxicity and produced increased embryo-foetal mortality, gross external, visceral, and skeletal malformations. It was concluded that gemtuzumab ozogamicin may cause foetal harm when administered to a pregnant woman.
Overall, there were no issues concerning the non-clinical pharmacology or the toxicology of gemtuzumab ozogamicin that negatively affected the overall benefit-risk assessment.

Efficacy

The clinical efficacy data presented in this application, was based on open-label, non-comparative studies. The antileukaemic activity of gemtuzumab ozogamicin was observed with a complete response rate (CR) of 13% in patients with a first relapse of AML following treatment [and complete response rate without full platelet recovery (CRp) was observed in 13% of patients]. The remission free survival (RFS) was 6.4 months for CR patients, including the consolidation therapy, and 3.8 months for the CR patients receiving no consolidation. The overall survival, measured as secondary endpoint, was a median 4.8 months for all patients (ranging from 13.1 months for CR patients, 9.7 months for CRp patients, to 2.8 months for patients who did not meet the criteria of CR/CRp). The survival was longer for patients who received haematopoietic stem cell transplantation as consolidation therapy (10.3 - 18.1 months) than for all other patients (1.3 - 11.5 months).
The applicant provided information to compare the efficacy of gemtuzumab ozogamicin in the target population, with the data reported in the scientific literature. The methodological limitations of such historical comparisons were acknowledged.

Safety

In phase II clinical trials, the most common grade 3 or 4 adverse drug reaction were fever, chills, nausea, vomiting and thrombocytopenia, and were seen in the majority of patients. The main safety issues related to the use of gemtuzumab ozogamicin consisted of severe and long-standing myelosuppression, infusion-related side effects (reversible and manageable), hepatotoxicity (reversible), and highly lethal veno-occlusive disease (VOD), especially when given in combination with HSCT. With the exception of hepatic abnormalities and myelosuppression, many of the adverse events reported after treatment with gemtuzumab ozogamicin occurred with rather low frequencies as compared to those observed with other treatments of leukaemia.

Risk-benefit assessment

The development of gemtuzumab ozogamicin for the re-induction treatment of CD33-positive acute myeloid leukaemia patients in first relapse who are not considered candidates for other cytotoxic chemotherapy was based on three single-arm clinical trials. Complete response, defined as no evidence of remaining tumour and haematological recovery within one month after remission induction treatment, was the primary endpoint. A complete response rate of 13% and a complete response rate without full platelet recovery of 13% were observed in patients with a median age of 61 years old, with a first relapse, and receiving Mylotarg as single agent.

The main limitations of this application were the modest proportion of CR and the lack of reliable data on valid clinical endpoints. In addition, according to CHMP guidelines, this full application should have been based on data generated by randomised controlled clinical trials rather than by open-label, non-comparative studies. The CHMP acknowledged the lack of established treatment for AML in first relapse, and the difficulties in designing randomised controlled trials in the absence of standard comparator. However, the CHMP considered that the claimed indication referred to a theoretical situation in which patients in first relapse would not be considered candidates for other cytotoxic chemotherapy. A randomised trial against the investigator's choice could be envisaged.
Therefore, the efficacy of gemtuzumab ozogamicin as compared to available treatment options was not demonstrated for the treatment of AML patients in first relapse who are not considered candidates for other cytotoxic chemotherapy. The clinical studies presented did not provide sufficient data to estimate the clinical benefit of gemtuzumab ozogamicin treatment in the claimed indication. During the assessment, the CHMP consulted the oncology Scientific Advisory Group (see CHMP questions and SAG responses in "Discussion on clinical efficacy" section). The outcome of the discussion was conveyed to the Committee and discussed.

Important identified risks with gemtuzumab ozogamicin were severe and long-standing myelosuppression, infusion-related side effects and hepatotoxicity, including irreversible and highly lethal veno-occlusive disease (VOD), especially when given in combination with HSCT.

Randomised phase III trials to assess the efficacy and safety of gemtuzumab ozogamicin when used as a first-line anti-leukaemic agent are ongoing.

The benefit risk balance of gemtuzumab ozogamicin in re-induction treatment of CD33-positive acute myeloid leukaemia patients in first relapse who are not candidates for other intensive re-induction chemotherapy regimens (e.g. high-dose ARA-C) is not considered favourable due to the following grounds:

- Only a small proportion of complete responders were observed in the clinical trials and the efficacy in terms of duration of remission, progression-free survival and overall survival is difficult to quantify in the absence of randomised controlled trial with single-agent gemtuzumab ozogamicin.
- Based on the available clinical efficacy results, the clinical benefit of the treatment with gemtuzumab ozogamicin is not established for the target population.
- Treatment with gemtuzumab ozogamicin toxicity includes severe and long-standing myelosuppression, infusion-related side effects, liver toxicity and veno-occlusive disease.
- The clinical benefit of the treatment with gemtuzumab ozogamicin is not established and therefore, the benefit-risk balance of the use of gemtuzumab ozogamicin in the claimed indication cannot be considered positive.

Similarity with authorised orphan medicinal products

In this application, the Applicant has provided arguments discussing the issue of similarity, in the context of Commission Regulation (EC) No 847/2000, regarding the orphan medicinal product Trisenox (arsenic trioxide) authorised in the EU for the treatment of acute promyelocytic leukaemia.

The CHMP concluded that:

- a marketing authorisation for the medicinal product Trisenox containing arsenic trioxide for induction of remission and consolidation in adult patients with relapsed/refractory acute promyelocytic leukaemia (APL) exists with orphan market exclusivity.

- gemtuzumab ozogamycin and arsenic trioxide are considered not to be similar with regards to the mechanism of action since they act on different pharmacodynamic targets.

- gemtuzumab ozogamicin is not structurally similar to arsenic trioxide.

Therefore, the CHMP considered Mylotarg not to be similar to any of the authorized orphan medicinal products (as defined in Art. 3 of Commission Regulation (EC) No 847/2000) for a condition relating to the proposed therapeutic indication.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by majority decision that the risk-benefit balance of Mylotarg in the re-induction treatment of treatment of CD33-positive acute myeloid leukaemia patients in first relapse who are not candidates for other intensive re-induction chemotherapy regimens (eg, high-dose ARA-C) was unfavourable and therefore did not recommend the granting of the marketing authorisation.

2.7 Re-examination of the CHMP opinion of 20 September 2007

Following the CHMP conclusion that the risk/benefit balance of gemtuzumab ozogamicin in the re-induction treatment of treatment of CD33-positive acute myeloid leukaemia patients in first relapse who are not candidates for other intensive re-induction chemotherapy regimens (eg, high-dose ARA-C) was unfavourable, the applicant submitted detailed grounds for the re-examination of the grounds for refusal. The applicant presented a number of arguments regarding the grounds for refusal.

The applicant presented in writing and at an oral explanation a number of additional analyses of the pooled clinical trials data, including responder analyses, subgroup analyses and survival analyses censoring for further treatments. The applicant stated that the observed CR/CRp rate was of benefit and associated with clinical improvement, and argued that a randomized controlled trial of Mylotarg monotherapy has not been feasible in the target indication. The applicant considered that the target population as defined in a revised indication was adequately represented in the clinical trials and that the safety and tolerability profile for these patients was comparable to that seen in the overall population. The applicant argued that among the side effects of gemtuzumab ozogamicin, infusion related effects, liver toxicity, as well as the risk of veno-occlusive disease have been recognized and may be mitigated by preventive measures such as the use of corticosteroids for infusion-related syndrome as in other treatments with monoclonal antibodies, by avoiding gemtuzumab ozogamicin treatment in patients with previous transplant or liver disease, and by exercising caution in the use of concomitant hepatotoxic drugs. Furthemore, the applicant commented that the more advantageous aspects of the safety profile of gemtuzumab ozogamicin include no drug-induced alopecia, low rate of severe mucositis, low rate of cardiac, renal, gastrointestinal, and neurologic events, and relatively low rate of infection. The applicant stated that the results of the gemtuzumab ozogamicin studies indicate clinical benefit with a positive benefit/risk balance in the target population.

Following a request from the applicant at the time of the re-examination, the CHMP convened a Scientific Advisory Group (SAG) inviting the experts to provide their views on the CHMP grounds for refusal, taking into account the applicant's response. The SAG considered that there was no convincing evidence in the applicant's grounds for re-examination that would change the grounds for refusal. The SAG argued that one of the main problems with the data submitted is the fact that the trials were not randomized versus a suitable control (e.g., investigator's choice). Furthermore, the pivotal trials with gemtuzumab included an ill-defined population, which in many cases could have been exposed to intensive re-induction chemotherapy. This population does not correspond to the claimed indication. Because the studies and claimed populations are different, it is impossible to extrapolate the results observed to the claimed indication. Thus, based on the data presented, the SAG concluded that it is impossible to establish the efficacy and safety of gemtuzumab in a population that truly consists of patients in first relapse who are not candidates for other intensive re-induction chemotherapy regimens (e.g., high-dose ARA-C). Nevertheless, a number of haematologists in the group expressed strong beliefs about the usefulness of this active compound for some AML patients in particular situations. However, the exact population for which they would currently use gemtuzumab remains very difficult to define, as this requires an individual patient's assessment of available options, including various re-induction regimens and types of HSCT, which are not scientifically established. For instance, frail patients with important co-morbidities that cannot tolerate high-dose chemotherapy yet sufficiently fit to tolerate the gemtuzumab associated toxicity might be considered for gemtuzumab on a case by case basis. It was also agreed that this would to a large extent depend on the haematologists attitude to use more or less aggressive treatments. However, it was agreed that this is based on expert judgement and not hard evidence and that the applicant has not defined clearly what could be the target population, or presented data to support the efficacy in a suitable target population.

The CHMP also requested advice from the SAG *on the following specific issues*

What is the value of re-induction treatment (pre-transplantation) in relapsed AML? I.e., if a cohort of AML patients in first relapse who are eligible for HSCT were re-induced with Mylotarg and 35% achieved a CR/CRp, is it probable that the cohort as a whole would come out better post-transplantation than if they were all transplanted up-front?

The SAG agreed that currently, it seems reasonable to assume, based on clinical and pharmacological arguments, and conflicting results from published research, that re-induction is beneficial in case of subsequent transplantation. It is possible that re-induction is really an important factor associated with

important clinical endpoints, or that at least it is useful to select patients that will most benefit form subsequent HSCT. Concerning a theoretical cohort of patients in first relapse eligible for HSCT, it is impossible to speculate the effect of gemtuzumab treatment on the final outcome. To some extent this situation is unrealistic because patients eligible for HSCT are most likely candidate for reinduction treatment with more effective combination regimens.

Are there relapsed AML patients who are not suitable for re-induction with chemotherapy but would at a later stage (post successful re-induction with Mylotarg) be suitable for HSCT?

The experts agreed that it is difficult to envisage a situation where patients are not suitable for re-induction chemotherapy but patients are suitable for HSCT after successful re-induction with Mylotarg. At least in theory, it is possible to imagine that there are rare situations where patients in full blown relapse with very poor clinical condition due to the leukaemic multiorgan infiltration itself might achieve a complete remission after some reduced intensity chemotherapy or monotherapy. If this was followed by a surprisingly good improvement in organ function and performance status this could at least in theory allow HSCT. Therefore, at least in theory, there might be some rare patients not suitable for re-induction with high dose chemotherapy but successfully treated with Mylotarg that could receive the RIC transplant owing to this response.

In patients with relapsed AML, not being candidates for intensive chemotherapy, is the proportion of CR/CRp observed with Mylotarg a reliable predictor of an overall favourable effect in all treated patients (ITT)?

According to the SAG, concerning the 35% of CR/CRp, it should be noted that these results are based on patients that in many cases could have been exposed to intensive re-induction chemotherapy. It is impossible to speculate what would be the proportion of CR/CRp observed with gemtuzumab in a population that truly consists of patients with a worse prognosis who are not candidates for other intensive re-induction chemotherapy regimens (e.g., high-dose ARA-C). Although traditionally CR/CRp is an endpoint for activity, it is also a relevant clinical benefit endpoint, provided that the response is of clinically significant duration. Of course, there should not be a detriment in terms of overall survival and progression-free survival, so that this endpoint should not be looked at in isolation. However, it is not known what would be the proportion of CR/CRp associated with gemtuzumab in the claimed indication or in a suitable indication, which definition remains elusive. Furthermore, this efficacy endpoint needs to be weighted against the observed toxicities which are significant.

Overall conclusion on grounds for re-examination

The applicant presented its grounds for reexamination and discussed them with the CHMP during an oral explanation and revised the claimed indication to better reflect the population in which the applicant claimed that a positive benefit risk had been demonstrated, namely for re-induction treatment of CD33-positive AML adult patients in first relapse who are not candidates for other intensive re-induction chemotherapy regimens (e.g. high-dose Ara-C) and meet at least one of the following criteria: duration of first remission $\leq$12 months, or age $\geq$60 years.

The CHMP assessed all the detailed grounds for re-examination and argumentations presented by the applicant and considered the views of the Scientific Advisory Group. The CHMP acknowledged that a number of haematologists and researchers have great interest in the product and in further studying its effects but was of the opinion that the data submitted in the current application do not allow to conclude that the clinical efficacy of Mylotarg has been demonstrated in the applied indication.

The CHMP maintained the view that only a small proportion of complete responders were observed in the clinical trials and the efficacy in terms of duration of remission, progression-free survival and overall survival is difficult to quantify in the absence of randomised controlled trial with single-agent gemtuzumab ozogamicin. The CHMP maintained the view that Based on the available clinical efficacy results, the clinical benefit of the treatment with gemtuzumab ozogamicin is not established for the target population. The CHMP also maintained the view that treatment with gemtuzumab ozogamicin toxicity includes severe and long-standing myelosuppression, infusion-related side effects, liver toxicity and veno-occlusive disease, and that because the clinical benefit of the treatment with gemtuzumab ozogamicin is not established, the benefit-risk balance of the use of gemtuzumab ozogamicin in the claimed indication cannot be considered positive.

GROUNDS FOR REFUSAL

Whereas

- Insufficient data have been presented to establish the clinical efficacy of gemtuzumab ozogamicin. Only a small proportion of complete responders were observed in the clinical trials and the efficacy in terms of duration of remission, progression-free survival and overall survival is difficult to quantify in the absence of randomised controlled trial with single-agent gemtuzumab ozogamicin.
- Based on the available clinical efficacy results, the clinical benefit of the treatment with gemtuzumab ozogamicin is not established for the re-induction treatment of CD33-positive AML adult patients in first relapse who are not candidates for other intensive re-induction chemotherapy regimens (e.g. high-dose Ara-C) and meet at least one of the following criteria: duration of first remission <12 months, or age >60 years.
- Treatment with gemtuzumab ozogamicin toxicity includes severe and long-standing myelosuppression, infusion-related side effects, liver toxicity and veno-occlusive disease.

the benefit-risk balance of Mylotarg in the claimed indication cannot be considered positive, and therefore the CHMP has recommended the refusal of the granting of the Marketing Authorisation for Mylotarg.