参考資料１

ひと、くらし、みらいのために
厚生労働省
Ministry of Health, Labour and Welfare

Press Release

（参考配布）

平成22年6月22日
医薬食品局安全対策課
（担当・内線）課長補佐　野村(2752)
鈴木(2791)
（代表電話）　03(5253)1111
（ダイヤルイン）　03(3595)2435

報道関係者　各位

マイロターグ®点滴静注用 5mg（一般名：ゲムツズマブオゾガマイシン）に関する米国での措置について

本日午後4時頃、**マイロターグ®点滴静注用 5mg の製造販売業者であるファイザー（株）より、別添のとおり本町記者クラブ※に投げ込み発表を行った旨の連絡**がありましたので、お知らせします。（※薬業業界紙の記者クラブ）

ファイザー株式会社

News Release

報道関係各位

2010年6月22日
ファイザー株式会社

マイロターグ®点滴静注用5mg（一般名：ゲムツズマブオゾガマイシン）に関する米国での措置について

2010年6月21日（米国現地時間）、米国ファイザー社と米国食品医薬品局（FDA）は、米国ファイザー社が2010年10月15日に米国内でのマイロターグの販売中止と自主的な承認の取下げを行うことをプレスリリースいたしました。以下に「米国での措置の経緯」および「日本における対応」に関してお知らせいたします。
本リリースの詳細につきましては http://www.pfizer.com/news/をご覧ください。

1. 米国での措置の経緯
米国では、市販後に本剤の臨床的有益性を確認する試験を実施して追加データを提出することを条件に、他の細胞傷害性化学療法の適応がない60歳以上のCD33陽性*急性骨髄性白血病**初回再発患者に対し、単剤療法で用いる薬剤として2000年に迅速承認されました。FDAとも協議の上、承認条件として実施された第Ⅲ相臨床試験（SWOG*** S0106試験）では、未治療の急性骨髄性白血病患者を対象に、標準的な初回寛解導入療法であるダウノルビシン塩酸塩とシタラビンの併用療法（DA療法）への本剤（GO）の併用効果、及び、大量シタラビン療法による地固め療法後の本剤の追加投与の効果を検討しました。この試験の中間解析において、有効性の改善がみられなかったため早期中止となりました。また、寛解導入期に生じた治療との関連性を否定できない致死的有害事象の発現率は、本剤併用群で有意に高いという結果でした。（DA+GO群：16/283=5.7%、DA群：4/281=1.4%, p=0.01）（2010年4月15日SWOGによる）

この結果に基づき、本剤の併用及び追加投与による臨床的有益性を確認できなかったため、米国ファイザー社は本剤の承認を自主的に取下げることを決定しました。

2. 日本における対応
日本において、本剤は、再発又は難治性のCD33陽性の急性骨髄性白血病の効能・効果にて承認されています。また、添付文書の警告欄にて他の抗悪性腫瘍薬と併用しないことを注意喚起しており、米国の上記臨床試験とは対象患者・使用方法が異なります。これまでも、添付文書の情報に基づき、医療機関においては本剤を慎重にお使いいただくようお願いしています。

製造販売後に得られた安全性情報では、全例調査（中間報告）633例中550例（86.9%）（CTCAE v3.0によるGrade3以上の副作用は490例（77.4%））に副作用が発現しており、本剤の特に注意が必要な副作用としては、静脈閉塞性肝疾患6.0%（Grade3以上4.7%）、感染症32.5%（Grade3以上26.2%）、出血13.6%（Grade3以上8.4%）等が見られています。

今回の米国で実施された臨床試験の対象患者・使用方法は、国内の承認の範囲とは異なっていますが、全例調査の解析結果や承認時の臨床試験の結果に基づいて、日本における本剤のリスク・ベネフィットを専門家、行政等の各署と協議の上、今後の国内の対応を決定する予定です。また本日より、弊社医薬情報担当者を通じて本剤を納入している医療機関に書簡を持参しての情報提供を開始いたしました。

* AML においては白血病細胞が CD33 抗原を細胞膜上に発現している場合を指します。CD33 は糖蛋白で、顆粒球、単球、一部の赤芽球と巨核球系の細胞膜表面上に発現しています。一方、正常造血幹細胞やリンパ系細胞では発現が認められていません。この CD33 は AML 白血病細胞の 80～90％の細胞表面に発現しています。竹下 他：腫瘍内科. 3(1). 62. 2009

** 急性骨髄性白血病（AML）は多能性造血幹細胞が腫瘍化した疾患です。AML では造血幹細胞は骨髄中で正常に分化することなく増殖するため、正常な血球産生が損なわれ、その結果、貧血、血小板減少、好中球減少を起こし、貧血症状、出血症状、重篤な感染症状などが出現します。神田：内科,97(6),1322,2006

*** Southwest Oncology Group の略です。米国で最も大きい癌の共同試験グループの 1 つです

以上

マイロターグ®の概要

【製品名】　マイロターグ®点滴静注用 5mg（MYLOTARG® Injection 5mg）

【一般名】　ゲムツズマブオゾガマイシン（遺伝子組換え）
Gemtuzumab Ozogamicin （Genetical Recombination）

【製造販売承認取得日】　2005 年 7 月 25 日

【販売開始】　2005 年 9 月 22 日 ＊旧販売名による

【製造販売】　ファイザー株式会社

【効能・効果】　再発又は難治性の CD33 陽性の急性骨髄性白血病

【用法・用量】　通常成人には、ゲムツズマブオゾガマイシン 1 回量 9mg/m² (たん白質量として表記) を 2 時間かけて点滴静脈内投与する。投与回数は、少なくとも 14 日間の投与間隔をおいて、2 回とする。

【推定使用患者数】　約 3000 人　（2005 年 9 月 22 日～2010 年 6 月 16 日）
【直近 3 ヶ月の推定使用患者数】　約 160 人（2010 年 4 月 1 日～6 月 16 日）

——この件に関するお問い合わせ先——
ファイザー株式会社　製品広報部 岩瀬　欣司
電話：03-5309-7395　E-mail：kinji.iwase@pfizer.com

参考資料 2-1

U.S. Department of Health & Human Services

U.S. Food and Drug Administration

Home > News & Events > Newsroom > Press Announcements

News & Events

FDA NEWS RELEASE

For Immediate Release: June 21, 2010
Media Inquiries: Erica Jefferson, 301-796-4988, erica.jefferson@fda.hhs.gov
Consumer Inquiries: 888-INFO-FDA

FDA: Pfizer Voluntarily Withdraws Cancer Treatment Mylotarg from U.S. Market

Pfizer Inc. today announced the voluntary withdrawal from the U.S. market of the drug Mylotarg (gemtuzumab ozogamicin) for patients with acute myeloid leukemia (AML), a bone marrow cancer. The company took the action at the request of the U.S. Food and Drug Administration after results from a recent clinical trial raised new concerns about the product's safety and the drug failed to demonstrate clinical benefit to patients enrolled in trials.

Mylotarg was approved in May 2000 under the FDA's accelerated approval program. This program allows the agency to approve a drug to treat serious diseases with an unmet medical need based on a surrogate endpoint – a laboratory measurement or a physical sign used as a substitute for a clinically meaningful endpoint that directly measures how a patient feels, functions, or survives.

Under accelerated approval, the company is required to conduct additional clinical trials after approval to confirm the drug's benefit. If those trials fail to confirm clinical benefit to patients, or if the company does not pursue the required confirmatory trials with due diligence, the FDA can withdraw the drug from the market using expedited procedures.

Mylotarg was approved to treat patients ages 60 years and older with recurrent AML who were not considered candidates for other chemotherapy. The initial approval was based on the surrogate endpoint of response rate (i.e., the percentage of patients whose leukemia decreased or disappeared in laboratory tests), observed in 142 patients with AML across three clinical trials.

A confirmatory, post approval clinical trial was begun by Wyeth (now Pfizer) in 2004. The trial was designed to determine whether adding Mylotarg to standard chemotherapy demonstrated an improvement in clinical benefit (survival time) to AML patients. The trial was stopped early when no improvement in clinical benefit was observed, and after a greater number of deaths occurred in the group of patients who received Mylotarg compared with those receiving chemotherapy alone.

At initial approval, Mylotarg was associated with a serious liver condition called veno-occlusive disease, which can be fatal. This rate has increased in the postmarket setting.

"Mylotarg was granted an accelerated approval to allow patient access to what was believed to be a promising new treatment for a devastating form of cancer," said Richard Pazdur, M.D., director, Office of Oncology Drug Products, part of FDA's Center for Drug Evaluation and Research. "However, a confirmatory clinical trial and years of postmarketing experience with the product have not shown evidence of clinical benefit in patients with AML."

As a result of the withdrawal, Mylotarg will not be commercially available to new patients. Patients who are currently receiving the drug may complete their therapy following consultation with their health care professional. Health care professionals should inform all patients receiving Mylotarg of the product's potential safety risks.

Following the withdrawal, any future use of Mylotarg in the United States will require submission of an investigational new drug application to FDA.

Mylotarg is manufactured by New York City-based Pfizer.

For more information:

- Pfizer: Mylotarg Withdrawal[1]
- FDA: Access to Investigational Drugs[2]
- FDA: Office of Oncology Drug Products[3]

#

RSS Feed for FDA News Releases[4] [what is RSS?[5]]

Links on this page:

1. http://www.pfizer.com
2. http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/AccesstoInvestigationalDrugs/default.htm
3. http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm
4. http://www.fda.gov/AboutFDA/ContactFDA/StayInformed/RSSFeeds/PressReleases/rss.xml
5. http://www.fda.gov/AboutFDA/ContactFDA/StayInformed/RSSFeeds/ucm144575.htm

参考資料 2-2

Dear Healthcare Professional Letter

Pfizer Prepares for Voluntary Withdrawal of U.S. New Drug Application and for Discontinuation of Commercial Availability of Mylotarg for Relapsed Acute Myeloid Leukemia

IMPORTANT PRESCRIBING INFORMATION

June 21, 2010

Dear Healthcare Professional,

Re: Mylotarg® (gemtuzumab ozogamicin for Injection) for patients with CD33+ acute myeloid leukemia (AML) in first relapse who are 60 years of age or older and who are not considered candidates for other cytotoxic chemotherapy.

Pfizer would like to inform you of an important outcome for Mylotarg in the U.S. resulting from the failure of a required post-approval study to confirm the drug's clinical benefit. This study was stopped early based on interim results from the study showing no evidence of improved efficacy for patients treated with Mylotarg in addition to chemotherapy for previously untreated Acute Myeloid Leukemia (AML) (Southwest Oncology Group Web site. https://swog.org/Visitors/Spring10GpMtg/ROS1004.asp. Accessed June 17, 2010). The study also showed, in patients evaluable for induction toxicity, the fatal induction toxicity rate was significantly higher in the study arm containing Mylotarg combined with induction chemotherapy than the arm using chemotherapy alone (i.e. without Mylotarg).

After discussions with the U.S. Food and Drug Administration (FDA), Pfizer will be discontinuing commercial availability of Mylotarg and will be voluntarily withdrawing the New Drug Application (NDA) for Mylotarg in the United States effective October 15, 2010.

Patients who are currently taking Mylotarg and those patients who have been prescribed Mylotarg may continue their course of therapy, in consultation with their physicians. However, Pfizer recommends that no new patients in the U.S. be prescribed Mylotarg. Future use of Mylotarg for new patients in the U.S. will require physician submission of an Investigational New Drug (IND) application to the FDA.

Discussions are continuing with FDA to manage the orderly discontinuation of Mylotarg from commercial availability while ensuring continued access to the drug for your patients currently receiving the drug under the US labeled indication or through participation in approved clinical trials during this transition period up to October 15, 2010.

Data Summary:

PE MYT00006

Mylotarg® (gemtuzumab ozogamicin for Injection) was approved in the U.S. as a single agent treatment for patients with CD33 positive acute myeloid leukemia (AML) in first relapse who are 60 years of age or older and who are not considered candidates for other cytotoxic chemotherapy.

The approval of single agent Mylotarg in the U.S. was granted under FDA's accelerated approval regulations (Subpart H) based on overall response rate in three non-comparative studies. Accelerated approval is subject to the requirement to submit additional data to confirm clinical benefit. The required post approval study (SWOG Study S0106) combining Mylotarg with chemotherapeutic agents, daunorubicin and cytosine arabinoside, versus the same chemotherapy agent combination without Mylotarg in first-line AML patients under the age of 61 was conducted to confirm clinical benefit for Mylotarg. A total of 627 patients were enrolled in this study.

The decision to voluntarily withdraw the NDA is based on data from SWOG Study S0106 which failed to confirm clinical benefit. This study was stopped early based on interim results from the study showing no evidence of improved efficacy for patients treated with Mylotarg in addition to chemotherapy for previously untreated AML. Additionally, the fatal induction toxicity rate was significantly higher in the daunorubicin and cytosine arabinoside + Mylotarg arm (16/283=5.7% vs. 4/281=1.4%, P=0.01) (SWOG Update, April 15, 2010).

A second Phase 3 study (AML 15) enrolled over 1100 patients and evaluated the addition of Mylotarg to induction and/or consolidation chemotherapy in the first-line treatment of patients of ages 0-70 with AML. This study also failed to show improvement in relapse-free survival or overall survival in the intent to treat population with the addition of Mylotarg. Of note, the addition of Mylotarg to the induction chemotherapy treatment regimen did not add significant additional toxicity (Burnett et al., 2010, N. Engl. J. Med. submitted).

Although these studies did not confirm clinical benefit, it is Pfizer's view that the results do not directly impact the risk/benefit profile of Mylotarg in its approved indication as a single agent. While Pfizer is disappointed by the recent first line combination Phase 3 study results, we remain committed to provide Mylotarg in the near future to U.S. patients currently receiving the drug as agreed upon with the FDA.

For more information about Mylotarg, please contact Pfizer Medical Information at **1-800-438-1985 or www.pfizer.com**. We hope you find this information helpful in understanding this subject so you can continue to appropriately treat your patients.

Sincerely,

Signed

Pfizer Inc

PE MYT00006

For immediate release:
June 21, 2010

Media Contact:
Curtis Allen
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Suzanne Harnett
(212) 733-8009

Pfizer Prepares For Voluntary Withdrawal Of U.S. New Drug Application And For Discontinuation Of Commercial Availability Of Mylotarg®

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Required Post-Marketing Study did not Confirm Clinical Benefit of Mylotarg

\- - -

Pfizer to Ensure Continued Access for Current Mylotarg Patients

NEW YORK, N.Y., June 21 - Pfizer Inc. announced today that based on discussions with the U.S. Food and Drug Administration (FDA), it will be discontinuing commercial availability of Mylotarg® (gemtuzumab ozogamicin for Injection) (used for the treatment of relapsed acute myeloid leukemia (AML)) in the United States and that it will be voluntarily withdrawing the new drug application (NDA) for Mylotarg effective October 15, 2010.

The approval of single agent Mylotarg in the U.S. was granted under FDA's accelerated approval regulations based on overall response rate in three non-comparative studies and required submission of additional data to confirm clinical benefit. The required post-approval study (SWOG S0106) combining chemotherapy and Mylotarg did not demonstrate improved survival compared with chemotherapy alone in patients with previously untreated AML.

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Additionally, among all patients evaluable for early toxicity the fatal induction toxicity rate was significantly higher in subjects given the combination of standard induction chemotherapy and Mylotarg than in those treated with chemotherapy alone. After extensive discussions with the FDA, Pfizer has decided to withdraw the NDA effective October 15, 2010.

"We are disappointed that the study did not confirm the clinical benefit of Mylotarg. Our primary concern is for patients who suffer from AML, which remains a very serious and difficult-to-treat disease with limited treatment options. We advise patients to contact their physicians for further information," said Dr. Mace Rothenberg, senior vice president of clinical development and medical affairs for Pfizer Oncology Business Unit.

Patients who are currently taking Mylotarg and those patients who have been prescribed Mylotarg may continue their course of therapy, in consultation with their physicians. However, Pfizer recommends that no new patients in the U.S. be prescribed Mylotarg. Future use of Mylotarg for new patients in the U.S. will require physician submission of an Investigational New Drug (IND) application to the FDA.

The Company is also working with Health Authorities outside the U.S. and will keep patients, regulatory authorities, investigators and clinicians informed about FDA actions and appropriate next steps for Mylotarg.

For further information please contact Pfizer Medical Information at 1-800-438-1985 or at www.pfizer.com.

Mylotarg® (gemtuzumab ozogamicin for Injection) was approved in the U.S. as a single agent for patients with CD33 positive AML in first relapse who are 60 years of age or older and who are not considered candidates for other cytotoxic chemotherapy. Patients

-more-

treated with Mylotarg receive one course of treatment that consists of two doses typically given 14 days apart.

AML is a relatively uncommon disease that affects approximately 13,000 new patients annually in the U.S. It is estimated that less than 2,500 patients receive Mylotarg annually in the U.S.

SWOG S0106 Post Approval Study

With the agreement of FDA, a Phase 3 randomized, comparative controlled trial (SWOG S0106) using Mylotarg in combination with other chemotherapeutic agents (daunorubicin and cytosine arabinoside) versus chemotherapy alone in first-line AML patients under the age of 61 was conducted to confirm clinical benefit for Mylotarg. A total of 627 patients were enrolled in this study. Although SWOG S0106 did not confirm the clinical benefit, the results do not directly impact the risk/benefit profile of Mylotarg in its approved indication as a single agent. Additionally, among all patients evaluable for early toxicity, the fatal induction toxicity rate was significantly higher in the daunorubicin and cytosine arabinoside + Mylotarg arm compared to the daunorubicin and cytosine arabinoside arm (16/283=5.7% vs. 4/281=1.4%, P=0.01).

About Mylotarg® (gemtuzumab ozogamicin for Injection)

Important safety information:

Mylotarg should be administered under the supervision of physicians experienced in the treatment of acute leukemia and in facilities equipped to monitor and treat leukemia patients.

There are no controlled trials demonstrating efficacy and safety using Mylotarg in combination with other chemotherapeutic agents. Therefore, Mylotarg should only be used as a single agent chemotherapy and not in combination chemotherapy regimens outside

-more-

clinical trials. Severe myelosuppression occurs when Mylotarg is used at recommended doses.

Mylotarg administration can result in severe hypersensitivity reactions (including anaphylaxis), and other infusion-related reactions which may include severe pulmonary events. Infrequently, hypersensitivity reactions and pulmonary events have been fatal. In most cases, infusion-related symptoms occurred during the infusion or within 24 hours of administration of Mylotarg and resolved.

Mylotarg infusion should be interrupted for patients experiencing dyspnea or clinically significant hypotension. Patients should be monitored until signs and symptoms completely resolve. Discontinuation of Mylotarg (gemtuzumab ozogamicin for Injection) treatment should be strongly considered for patients who develop anaphylaxis, pulmonary edema, or acute respiratory distress syndrome. Since patients with high peripheral blast counts may be at greater risk for pulmonary events and tumor lysis syndrome, physicians should consider leukoreduction with hydroxyurea or leukapheresis to reduce the peripheral white count to below 30,000 per microliter prior to administration of Mylotarg.

Hepatotoxicity, including severe hepatic veno-occlusive disease (VOD), has been reported in association with the use of Mylotarg as a single agent, as part of a combination chemotherapy regimen, and in patients without a history of liver disease or hematopoietic stem-cell transplant (HSCT). (See WARNINGS and ADVERSE REACTIONS sections of the full Information.) Patients who receive Mylotarg either before or after HSCT, patients with underlying hepatic disease or abnormal liver function, and patients receiving Mylotarg in combinations with other chemotherapy may be at increased risk for developing severe VOD.

-more-

Death from liver failure and from VOD has been reported in patients who receive Mylotarg (gemtuzumab ozogamicin for Injection). Physicians should monitor their patients carefully for symptoms of hepatotoxicity, particularly VOD. These symptoms can include: rapid weight gain, right upper quadrant pain, hepatomegaly, ascites, elevations in bilirubin and/or liver enzymes. However, careful monitoring may not identify all patients at risk or prevent the complications of hepatotoxicity.

Mylotarg may cause fetal harm when administered to a pregnant woman. The reported rates of Grades 3 and 4 thrombocytopenia, neutropenia, anemia, and bleeding were 99%, 98%, 47%, and 15%, respectively. Twenty-eight percent of patients experienced severe infections, including sepsis (16%) and pneumonia (7%).
The most common adverse events were fever (85%), chills (73%), nausea (70%), vomiting (63%), asthenia (44%), diarrhea (38%), abdominal pain (37%), headache (35%), stomatitis (32%), dyspnea (32%), epistaxis (31%), hypokalemia (31%), anorexia (29%), sepsis (25%), constipation (25%), local reaction (25%), nonspecific rash (22%), herpes simplex (22%), and neutropenic fever (21%).

Mylotarg can produce a postinfusion symptom complex of fever and chills and less commonly hypotension and dyspnea during the first 24 hours after administration. Patients should receive diphenhydramine 50 mg po and acetaminophen 650-1000 mg po one hour before Mylotarg (gemtuzumab ozogamicin for Injection) administration. Two additional doses of acetaminophen 650-1000 mg po every four hours may be given. Vital signs should be monitored during infusion and for four hours following infusion.

Please see full prescribing information at:
http://www.wyeth.com/content/showlabeling.asp?id=119.

-more-

About Pfizer Oncology

Pfizer Oncology is committed to the discovery, investigation and development of innovative treatment options to improve the outlook for cancer patients worldwide. Our strong pipeline, one of the most robust in the industry, is studied with precise focus on identifying and translating the best scientific breakthroughs into clinical application for patients across a wide range of cancers, including breast, lung, prostate, sarcoma, melanoma, and various hematologic cancers. Pfizer Oncology has biologics and small molecules in clinical development and more than 200 clinical trials underway.

By working collaboratively with academic institutions, individual researchers, cooperative research groups, governments, and licensing partners, Pfizer Oncology strives to cure or control cancer with breakthrough medicines, to deliver the right drug for each patient at the right time. For more information please visit www.Pfizer.com.

# # # # #

参考資料 3

European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

London, 24 January 2008
Doc.Ref.: EMEA/CHMP/5130/2008

REFUSAL ASSESSMENT REPORT FOR MYLOTARG

International Nonproprietary Name:
gemtuzumab ozogamicin

Procedure No. EMEA/H/C/000705

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

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 75 23 70 51
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

PRODUCT INFORMATION

Name of the medicinal product:	Mylotarg
Applicant:	Wyeth Europa Ltd Huntercombe Lane South Taplow Maidenhead, Berks SL6 0PH United Kingdom
Active substance:	gemtuzumab ozogamicin
International Nonproprietary Name/Common Name:	gemtuzumab ozogamicin
Pharmaco-therapeutic group (ATC Code):	Monoclonal antibodies (L01XC05)
Therapeutic indication(s):	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.
Pharmaceutical form(s):	Powder for solution for infusion
Strength(s):	5 mg
Route(s) of administration:	Intravenous use
Packaging:	vial (glass)
Package size(s):	1 vial

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Wyeth Europa Ltd submitted on 07 December 2005 an application for Marketing Authorisation to the European Medicines Agency (EMEA) through the centralised procedure for Mylotarg, which was designated as an orphan medicinal product EU/3/00/005 on 18 October 2000. Mylotarg was designated as an orphan medicinal product in the following indication: treatment of acute myeloid leukaemia. The calculated prevalence of this condition was 0.66 per 10,000 EU.

The applicant applied for the following indication: treatment of CD33-positive acute myeloid leukaemia patients in first relapse who are not candidates for other cytotoxic chemotherapy, such as those who are 60 years of age or older.

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application contained a critical report addressing the possible similarity with authorised orphan medicinal product Trisenox.

Protocol Assistance:
The applicant received Protocol Assistance from the CHMP on 25 March 1999 and 1 March 2001. The Protocol Assistance pertained to clinical aspects of the dossier.

Licensing status:
Mylotarg has been given a Marketing Authorisation in the following countries:
Cyprus on 23 May 2001, Argentina on 29 December 2000, Brazil on 8 March 2001, Chile on 1 August 2001, Colombia on 24 January 2002, India on 15 September 2002, Israel on 30 June 2003, Japan 25 July 2005, Korea on 10 September 2004, Mexico on 11 September 2001, Singapore on 28 September 2001, south Africa on 11 December 2003, Thailand on 27 August 2002, USA on 17 May 2000, Venezuela on 19 August 2002.

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: **Jens Ersbøll** Co-Rapporteur: **Pasqualino Rossi**

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 7 December 2005.
- The procedure started on 28 December 2005.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 14 March 2006. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 17 March 2006.
- On 20 April 2006, the Biologics Working Party (BWP) adopted a recommendation to the CHMP for the list of questions related to quality aspects.
- During the meeting on 24-27 April 2006, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 27 April 2006.
- A clarification meeting with the Rapporteurs on the List of Questions was held at the EMEA on 31 May 2006.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 10 July 2006.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 7 September 2006.

- On 13 September 2006, the BWP adopted a recommendation to the CHMP for the list of outstanding issues related to quality aspects.
- During the CHMP meeting on 18-21 September 2006, the CHMP agreed on a list of outstanding issues to be addressed in writing and in an oral explanation by the applicant.
- A Scientific Advisory Group in Oncology meeting was convened at the EMEA on 30 November 2006 to address questions raised by the CHMP.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the list of outstanding issues related to quality aspects on 16 January 2007 identifying issues to be addressed at an oral explanation before the BWP.
- During the CHMP meeting on 22-25 January 2007 the Committee agreed to the request from the applicant to postpone the Oral explanation to February 2007.
- During the CHMP meeting on 19-22 February 2007 the Committee agreed to the request from the applicant to postpone the Oral explanation at the CHMP and BWP to April 2007.
- The applicant submitted the responses to the CHMP consolidated list of outstanding issues on 27 March 2007.
- The Rapporteurs circulated the updated Joint Assessment Report to all CHMP members on 3 April 2007.
- During the BWP meeting on 17 April 2007, outstanding quality issues were addressed by the applicant during an oral clarification before the BWP and the BWP adopted a recommendation to the CHMP on quality aspects and a list of post-marketing commitments on 18 April 2007 (Annex 11).
- During the CHMP meeting on 23-26 April 2007 the Committee agreed to an extension of timeframe to allow the assessment of the submitted quality and clinical data.
- The Rapporteurs circulated a further updated Joint Assessment Report to all CHMP members on 7 May 2007.
- During the CHMP meeting on 21-24 May 2007, the CHMP agreed on a second list of outstanding issues to be addressed in writing and in an oral explanation by the applicant.
- The Rapporteurs circulated an updated assessment report in preparation for the oral explanation to all CHMP members on 15 June 2007.
- During the CHMP meeting on 18-21 June 2007, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the CHMP meeting on 16-19 July 2007, the CHMP agreed on a third list of outstanding issues to be addressed in an oral explanation by the applicant and adopted a report on similarity of Mylotarg and Trisenox.
- The applicant submitted responses to the CHMP consolidated list of outstanding issues on 10 August 2007.
- The Rapporteurs circulated an updated assessment report on the responses to the CHMP third list of outstanding issues on 11 and 14 September 2007.
- During the CHMP meeting on 17-20 September 2007, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 17-20 September 2007 the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a Marketing Authorisation to Mylotarg on 20 September 2007.
- The CHMP opinion was received by the applicant on 28 September 2007.

1.3 Steps taken for the re-examination procedure

- The applicant submitted written notice to the EMEA on 17 October 2007 to request a re-examination of the Mylotarg CHMP Opinion of 20 September 2007.
- During its meeting on 15-18 October 2007, the CHMP appointed Tomas Salmonson as Rapporteur and David Lyons as Co-Rapporteur for the re-examination procedure.
- The detailed grounds for the re-examination request were submitted by the applicant on 27 November 2007.
- The re-examination procedure started on 28 November 2007.

- The Rapporteur's Assessment Report on the detailed grounds for the re-examination was circulated on 21 December 2007. The Co-Rapporteur's Assessment Report was circulated on 18 December 2007.
- During a meeting of the Scientific Advisory Group in Oncology on 11 January 2008, experts were convened to consider the grounds for re-examination.
- During the CHMP meeting on 21-24 January 2008, the grounds for refusal were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 21-24 January 2008, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a final negative Opinion recommending the refusal of granting a Marketing Authorisation for Mylotarg.

2. SCIENTIFIC DISCUSSION

2.1 Introduction

Acute myeloid leukemia

Acute myeloid leukemia (AML) is the most common type of acute leukemia in adults and accounts for ~80% of all cases of acute leukaemia [1]. Worldwide, there are approximately 260,000 new cases of AML each year [2]. With an average incidence of 1 to 3 cases per 100,000 individuals [2], roughly 7000 to 21,000 cases can be estimated per year in Europe. Incidence increases with age and peaks in adults 65 years of age or older [1]. Slightly more than half of all patients are ≥60 years of age [3]. Despite recent developments in understanding the scientific basis of AML and its treatment, there has been little progress in increasing the long-term survival rates in AML patients. If left untreated most patients with AML will die from their disease. If patients are treated, the 5-year survival rate from time of diagnosis is ~20% [4]. With standard treatments, there is a high rate of first remission for patients with de novo (previously untreated) AML, however, ~75% of these patients will ultimately suffer a relapse, in most cases within 2 years [5].

The basic therapeutic approach to AML treatment has changed little over the last 20 years. The approach classically involves 2 separate treatment phases:

(1) induction chemotherapy, with a standard regimen of 3 days of an anthracycline and 7 days of cytarabine, aims at inducing a temporary bone marrow hypoplasia and the regeneration of the normal haematopoietic clone.

(2) consolidation therapy, which consist of multiple courses of intensive consolidation therapy which can be haematopoietic stem cell transplantation (HSCT) or high or intermediate does of cytarabine, aims at reducing the undetectable burden of leukemic cells to a level low enough that long-term disease- free survival (ie, a cure) might be possible.

With standard induction chemotherapy, complete remission is obtained in nearly 70% of the patients [5-7]. For consolidation therapy, the most effective antileukemic approach is allogeneic stem cell transplantation (SCT). However, this technique carries a high risk of initial mortality and a significant risk of long-term morbidity associated with chronic graft-versus-host disease, which tends to offset the therapeutic benefits of a low likelihood of relapse. Chemotherapeutic-based approaches with or without autologous stem cell rescue can be performed relatively safely, but the risk of disease recurrence remains high. Patients with relapsed AML have a particularly poor prognosis. A number of cytotoxic agents and combination regimens have been used for salvage chemotherapy and remission rates from 20 – 70 % have been described. However, the period of remission lasts only typically between 4-6 months.

Currently, authorised drugs for the treatment of AML in the EU include daunorubicin, doxorubicin, cytararabine, mitoxantrone, all-trans-retinoic acid and arsenic trioxide.

About the product

Gemtuzumab ozogamicin (CMA-676) is a humanized (CDR-grafted) IgG4 isotype monoclonal antibody against the CD33 antigen (hP67.6) that is conjugated to a cytotoxic agent N-acetyl gamma calicheamicin dimethyl hydrazide (NAc-gamma calicheamicin DMH) via the bifunctional AcBut linker. The hP67.6 antibody (non-cytotoxic by itself) binds to the CD33 antigen, is internalised and, hence, delivers the calicheamicin derivative to the inside of the leukaemic cell [16-21]. The CD33 antigen is expressed on the external surface of normal and leukaemic myeloid cells, and leukaemic blasts in more than 80% of patients with acute myeloid leukaemia (AML), but not on normal precursor haematopoietic cells [10, 11]. The antibody linked to the conjugate is internalized into lysosomes, where acidification releases the NAc-gamma calicheamicin DMH moiety. The latter undergoes spontaneous reaction with reduced glutathione (GSH) within the cell, where it is activated and the anti-tumour effect can occur [12]. The calicheamicins are potent anti-tumour antibiotics that were initially identified by their ability to damage DNA in screening tests [13]. Their anti-tumour mechanism is thought to occur by binding to the minor groove in the DNA and producing site-specific

double-strand breaks by forming p-benzene diradical [14, 15]. This results in the death of the leukaemic cell.

Mylotarg was approved by the FDA, in the USA in May 2000 for the treatment of AML patients who suffer from a first relapse, are ≥60 years old and are not candidates for other cytotoxic chemotherapy. As a post-approval commitment, the applicant committed to carrying out a randomised consolidation study in de novo AML, which is still ongoing. Mylotarg was also approved in Japan in July 2005 for the indication of relapsed or refractory CD33 positive AML.

An Orphan Drug Designation based on significant benefit was issued 18 October 2000 for the treatment of Acute Myeloid Leukaemia (EU/3/00/005). The current proposed indication is within the designation.

2.2 Quality aspects

Introduction
Mylotarg (gemtuzumab ozogamicin) is a chemotherapy medicinal product containing a recombinant humanised IgG4 kappa antibody linked to calicheamicin, a cytotoxic anti-tumour antibiotic isolated from fermentation of a bacterium. The antibody portion of Mylotarg binds specifically to the CD33 antigen. This antigen is expressed on the surface of leukaemic blasts in more than 80% of patients with acute myeloid leukaemia (AML). Upon binding to the CD33 antigen, the calicheamicin-CD33 complex is internalised within the leukaemia cell and calicheamicin is released from the conjugate via hydrolysis in the lysosome. The released calicheamicin then binds to the minor groove of the DNA causing site-specific double-strand breaks via the formation of a p-benzene di-radical. This ultimately leads to cell death by apoptosis.

Active Substance

The active substance, gemtuzumab ozogamicin, is an antibody-targeted chemotherapeutic agent comprised of three different parts:
A. a humanised IgG4 monoclonal antibody (hereafter termed 'hP67.6') conjugated to
B. the cytotoxic agent N-acetyl gamma calicheamicin dimethyl hydrazide (NAc-gamma calicheamicin DMH) via
C. a bifunctional linker.
The hP67.6 antibody, which is non-cytotoxic by itself, is directed against the CD33 antigen.

1. hP67.6 monoclonal antibody drug substance intermediate

Manufacture
The monoclonal antibody ('hP67.6') is manufactured by an approved manufacturer in compliance with Good Manufacturing Practice (GMP).

The hP67.6 antibody is produced by humanisation of the anti-CD33 murine antibody hP67.6 by complementarity determining region grafting (CDR grafting). The resulting hP67.6 antibody is a genetically engineered human IgG4 kappa antibody, which contains sequences derived from the murine antibody in the antigen-binding region only to minimise human anti-murine antibody response. The IgG4 isotype was chosen because it has the longest circulating half-life of all isotypes and is least likely to participate in immune-mediated mechanisms such as complement fixation and antibody-dependent cellular toxicity.

The established cell banking system is adequate for the reliable manufacturing of a monoclonal antibody. Criteria for the establishment of new WCB were provided. The cell bank testing is adequate. The development of the cell line, the creation of the cell bank and its testing follow a scientifically sound scheme and were sufficiently described. Generally the requirements of the relevant guidelines are met.

Overall the control of source and starting materials has been adequately documented. Materials of animal/human origin used in the manufacturing process of hP67.6 are described below (in the section 'adventitious agents'). Overall, materials used in the manufacturing process are adequately controlled.

The transfected recombinant murine plasmacytoma cell line (designated as KD1) is grown as a suspension culture in a fed-batch process. The fermentation and harvest of hP67.6 antibody is straightforward and has been adequately described. The hP67.6 antibody purification process includes two chromatographic columns including a Protein A chromatography step). Viral inactivation is obtained by low pH treatment and viral DV50 nanofiltration. In-process controls, including control limits, are in place during fermentation, harvest and purification. The manufacturing process and in-process controls have been sufficiently described. Establishment of controls for critical steps and intermediates are described in detail.

Process validation studies were presented demonstrating that the full-scale hP67.6 fermentation and purification process can achieve lot-to-lot consistency and reproducibility. The contribution of each step of the purification process to the removal of impurities derived from the hybridoma cell line and the culture media has been demonstrated, showing a high and consistent removal of the impurities. Further, it has been shown, by a variety of methods, that the hP67.6 antibody integrity is not affected by the purification process.

A detailed and adequate rationale for the changes introduced to the manufacturing process during development has been provided. It has been shown that changes (change in cell line, introduction of viral filtration step and introduction of recombinant protein A resin) were without influence on the quality of the hP67.6 antibody.

The applicant presented a comprehensive structural and functional profile of the antibody, primarily obtained using a combination of chromatographic, electrophoretic and mass spectrometry (MS) techniques. Overall the hP67.6 antibody has bee carefully characterised using a wide range of methods.

Specifications

The analytical methods used in the release control of the hP67.6 antibody intermediate are to a great extent based on non- or semi-quantitative electrophoresis methods. More quantitative methods, such as chromatographic methods are only used to a limited extent. This is acceptable in view of the tests performed on the active substance, i.e. the conjugated antibody. The hP67.6 antibody characterisation study clearly revealed that several varying forms of the antibody exist as well as the presence of aggregated forms and charge variants (determined by isoelectric focusing). This variability is controlled to some extent at the level of the unconjugated hP67.7 antibody and further at the level of the conjugated antibody.

Non-compendial analytical methods used for release testing have been specifically validated for use with the hP67.6 antibody. Batch results from a total of 54 lots have been provided. The data from the batches have met the acceptance criteria of the product specification in place at the time the batches were manufactured.

The level of host cell proteins (HCP) is measured using a semi-quantitative western blot assay which has been sufficiently validated. The Applicant also performed a study with a quantitative ELISA method which confirmed the low levels of HCP found using the western blot assay. The Applicant provided a post-marketing commitment to implement the ELISA method for release of the antibody.

The analytical methods used for release testing of the hP67.6 antibody have been satisfactorily described and validated. The chosen test parameters and limits have been adequately justified with reference to development data, batch analysis and/or stability data.

Stability

The requested shelf life for the hP67.6 antibody is adequately supported by stability data.

2. Activated calicheamicin drug substance intermediate

Manufacture, specifications and stability
The activated calicheamicin intermediate is manufactured by an approved manufacturer.
The nomenclature, structure and general properties of the activated calicheamicin derivative have been described satisfactorily. Calicheamicin is obtained by bacterial fermentation and the manufacturers and the fermentation process with subsequent synthetic steps have been described satisfactorily. The producer microorganism and the raw materials used in the fermentation process and the subsequent synthetic steps are adequately controlled and adequate in-process controls have been established and control ranges are supported by satisfactory validation studies.

The molecular structures of the activated calicheamicin-derivative and related substances have been adequately characterised. The analytical methods used for release testing of activated calicheamicin have been satisfactorily described and validated and the presented batch analysis results indicate that the process is under control. The chosen test parameters and limits have been adequately justified on the basis of batch data and are acceptable. The in-house primary reference material has been adequately characterised and the chosen container closure system provides adequate protection for this substance. Satisfactory stability evaluation has been performed. The proposed re-test period and storage condition are acceptable, when the activated calicheamicin-derivative is stored using the proposed container closure system.

3. Gemtuzumab ozogamicin drug substance

The drug substance is manufactured and controlled by an approved manufacturer in compliance with GMP.

Manufacture
The drug substance gemtuzumab ozogamicin is formed when activated calicheamicin is added to a solution of hP67.6 antibody. The reaction, results in the covalent attachment of activated calicheamicin to the antibody. The resulting active substance consists of a mixture of conjugated and unconjugated hP67.6 antibody. The conjugated molecules differ in the number of calicheamicin moieties attached to the hP67.6 antibody.

Conjugation invariably leads to the formation of some undesired aggregated protein. Size exclusion chromatography is used to separate monomeric antibody conjugate from the aggregated material formed. Process derived impurities are separated from gemtuzumab ozogamicin during the purification process. Impurities are reduced to a low level during purification and are controlled by adequate release specifications.

Two materials of biological origin are used during the manufacture of gemtuzumab ozogamicin. These substances are produced from bovine milk of US origin and are adequately controlled (see also '*adventitious agents*').

Critical in-process controls as well as non-critical controls are specified for the conjugation and purification process to assure a consistent production of the drug substance.

Three consecutive production batches were manufactured to demonstrate that the process met validation acceptance criteria. The gemtuzumab ozogamicin drug substance process validation exercise was successfully completed, documenting the ability to consistently produce drug substance with predictable and acceptable product quality. The properties and consistency of the validation batches of drug substance upon manufacture were evaluated using a battery of release tests.

Gemtuzumab ozogamicin has been characterised structurally by spectroscopic, electrophoretic and chromatographic assays, and characterised functionally by ELISA and immunoassays. All characterisation testing was conducted on reconstituted Mylotarg drug product because of the limited stability of the drug substance. Data shows that the conjugation reaction does not change the antibody

structure, including the glycosylation. Likewise, it has been shown that binding of the monoclonal antibody to CD33 cells is not affected by the calicheamicin conjugation.

Comparability studies have been conducted to evaluate whether changes introduced to the manufacturing process had any impact on the quality of the drug substance. These changes were introduced in particular to optimise the conjugation process, to minimise aggregate formation, and to obtain higher yields. The conjugation reaction is influenced by several factors. The comparability studies cover the very first material produced up to commercial material and consist solely of release test results. Additional characterisation studies were not performed.

The drug substance consists of a mixture of unconjugated antibody and antibodies to which a varying number of calicheamicin moieties are linked. The number of conjugated calicheamicin moieties can vary. The presence of significant amounts of unconjugated antibody in the drug substance was recognised late in the development program after the pivotal clinical trials had been completed and the manufacturing process had been validated, i.e. after 2001. As such, the unconjugated fraction was not tracked in the clinical batches nor was it considered during process development. Therefore the data available from the currently manufactured batches cannot be linked to the material used in clinical trials performed prior to 2001 with regard to distribution of conjugated and un-conjugated hP67.6 antibodies. Full comparison of batches (n=78) produced after 2001, when the test for low conjugation fraction was introduced, showed good consistency with respect to the low conjugation fraction in the commercial product and it is considered that the manufacturing process guarantees consistency in this respect.

As a test for low conjugated antibodies was not available at time of production of material for the clinical trials it can not be assured that the level of low conjugated antibody was the same in the material used in non-clinical and clinical studies as it is in the product to be placed on the market. However, in general, the comparability study covering the very first non-clinical and early clinical batches, clinical batches and the first production batches up to the current production batches shows reasonably consistent release test results among the batches despite differences in the production process. SDS-PAGE analysis shows a higher purity and a lower level of aggregates in the commercial material compared to the very first batches used in non-clinical and early clinical material. On the other hand, different concentrations of calicheamicin have been used in the conjugation reaction in the past compared to the commercial production process. At least in theory, the difference in concentrations of calicheamicin could have an impact on the calicheamicin conjugation level. In this respect it is noted that the proposed specification for the low conjugated fraction has been in place for several years for commercial lots placed on the market in the USA Since the assessment of the clinical efficacy and safety data did not reveal any signals related to the level of unconjugated antibody, there is sufficient reassurance over the clinical efficacy and safety with respect to the level of unconjugated antibody.

Specifications

The analytical procedures used for release testing include state-of-the-art methods such as sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE), isoelectric focusing (IEF), high pressure liquid chromatography (HPLC) and enzyme linked immunosorbant assay (ELISA). These methods have been appropriately validated and are adequate for the assessment of the active substance. The set of specification and limits were adequately justified on the basis of data obtained from numerous batches. All results were within specifications and the results are consistent, except for the very first non-clinical and clinical batches, which had a lower level of purity as shown by SDS-PAGE and a higher level of aggregates and unconjugated calicheamicin.

The specifications include aggregate and unconjugated calicheamicin ozogamicin as well as microbiological (endotoxins by LAL and bioburden) and general tests such as protein content. The non-reducing SDS-PAGE and IEF methods used for identification of the drug substance are only qualitative and were considered insufficient. Therefore, following the request from CHMP the applicant have introduced tests for peptide mapping and oligosaccharide profiling to assure consistency of antibody variants. Potency is tested using a cytotoxicity assay and an immunoaffinity antigen binding ELISA.

The specifications proposed for gemtuzumab ozogamicin are considered appropriate to ensure sufficient quality with respect to purity and level of impurities.

Stability
Gemtuzumab ozogamicin drug substance has limited stability and it is therefore shipped to the lyophilisation site immediately after manufacture prior to the completion of all testing and formal release. Release of the resulting drug product batches is contingent upon acceptable results for drug substance release testing.

Medicinal Product
Mylotarg is a sterile, white, preservative-free lyophilised powder containing 5 mg of gemtuzumab ozogamicin in a 20 ml amber vial. The inactive ingredients are Dextran 40, sucrose, sodium chloride, monobasic and dibasic sodium phosphate. The finished product should be reconstituted with 5 ml of sterile water for injections which is not provided with the product. The reconstituted product is administered as an infusion following dilution in a solution of 0.9% sodium chloride.

Pharmaceutical Development
The development of the lyophilised formulation has been thoroughly described and the rationale for the selection of the formulation and container configuration has been adequately addressed and justified.

Manufacture

The finished product is manufactured by an approved manufacturer (fill and lyophilisation by Ben Venue Laboratories, Inc., USA and packaging by Wyeth Farma SA, Spain) in compliance with GMP. The manufacturing process together with in-process controls has been adequately described. Following the request from CHMP during evaluation, an in-process control test on residual moisture on the lyophilised powder was introduced and the limits for the in-process controls performed during lyophilisation (i.e. temperature, time and pressure) have been stated. The critical steps are defined and controlled and validation data of the critical steps, i.e. sterile filtration, aseptic filling, holding time from start of sterile filtration to start of lyophilisation and container closure system have been provided and are acceptable.

The results from the analysis of production batches show that the manufacturing process used is capable of consistently producing drug product of the required quality.
No new impurities are formed during manufacture and the purity/impurity profile of the drug product is comparable to that of the drug substance.

Product specification

Specifications and release criteria for Mylotarg have been established to ensure identity, purity, potency, quality, and safety. Many of the analytical procedures used for testing the drug product are the same as the drug substance. Additional testing on drug product includes moisture content, uniformity of content, and sterility. Following the request from CHMP during evaluation, the tests for extractable volume, opalescence and osmolality were added. Overall, all methods for release testing of the drug product have been adequately described, justified and validated. The proposed limits are considered acceptable.

Stability
The stability of the drug product has been extensively investigated on clinical and pilot batches. The data show that the drug product is stable for the proposed shelf-life of 36 months at 2-8°C. The data from clinical and pilot batches are comparable and indicate that the commercial batches (manufactured at twice the scale) have a comparable stability. Photostability data shows that the drug product should be protected from light. Simulated clinical admixture infusion studies support a maximum allowed time of 20 hours for product reconstitution, dilution, and administration (through the completion of infusion).

Microbiological aspects were not investigated in the simulated clinical admixture infusion studies therefore, from a microbiological perspective, the product should be used immediately after reconstitution and dilution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 20 hours for product reconstitution, dilution, and administration (through the completion of infusion)

Adventitious agents
Materials of animal/human origin used in the manufacturing process of the hP67.6 antibody and gemtuzumab ozogamicin have been properly documented.

Compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products (EMEA/410/01 Rev. 2) has been demonstrated.

It is noteworthy that the hP67.6 antibody was originally manufactured using one material of animal origin obtained from plasma pools not tested in compliance with EU requirements. The selection and screening of donors used for the production of this material was not clearly specified: epidemiological data was not presented, the overall safety strategy was not satisfactorily detailed to ensure traceability, test kits were not described nor validated, etc. The Applicant committed to not place Mylotarg produced with this material onto the EU market. Only Mylotarg produced with a material derived from plasma which complies with EU requirements and for which a plasma master file is available would be put on the EU market.

The viral validation studies have demonstrated efficient and consistent removal of viruses The combined reduction capacity of the chromatographic columns demonstrated an overall virus reduction of at least 4 $\log_{10}$ .for small non-enveloped viruses. Based on the overall data presented; i.e. control of starting materials, control during the process and virus validation, the risk of virus transmission to patients receiving Mylotarg is remote.

2.3 Non-clinical aspects

Introduction

The pharmacology of gemtuzumab ozogamicin was investigated *in vitro* and *in vivo*. Pharmacodynamic and pharmacokinetic studies were not conducted according to GLP standards.

The toxicity studies in rats and cynomolgus monkeys and the reproductive and developmental toxicity studies in rats were conducted according to GLP standards, as claimed by the applicant.

Pharmacology

In vitro studies evaluated the cytotoxicity of gemtuzumab ozogamicin on CD33+ and CD33- cells in tissue culture assays, and comparisons were made with control conjugates with an antibody that does not recognize the CD33+ cells. Ex vivo, colony-forming assays were conducted with bone marrow samples from AML patients and with control conjugates. The behaviour of the antibody-calicheamicin conjugate in the body, the specificity of its anti-tumour activity and the extent to which it may affect normal cells was assessed in vivo. The potential for gemtuzumab ozogamicin to affect vital body systems (ie, cardiovascular, central nervous system [CNS], gastrointestinal, hepatic, and renal) has been investigated.

- Primary pharmacodynamics

The hP67.6 antibody component of gemtuzumab ozogamicin was found to bind only to $CD33^+$ cells and was non-cytotoxic in tissue culture. As a human monoclonal antibody of the IgG4 isotype class, neither complement-binding nor antibody-dependent cellular cytotoxicity (ADCC) was expected or observed in test animals.

In vitro, antigen binding specificity of gemtuzumab ozogamicin was indistinguishable from that of the uncoupled hP67.6 antibody. The relative affinity of four GMP batches of gemtuzumab ozogamicin was determined by competitive binding of gemtuzumab ozogamicin *versus* radio-labelled mP67.6 antibody to $CD33^+$ HEL 92.1.7 cells. Competitive binding was in the order of 10% of that of the hP67.6 antibody, which is within the limit of experimental error for this method. In terms of tissue specificity, neither gemtuzumab ozogamicin nor hP67.6 antibody exhibited any unexpected or unspecific binding to normal human tissues tested. In addition to HEL92.1.7 cells, hP67.6 antibody also stained microglia cells in the cerebellum, which are considered to be of mesodermal rather than neuroectodermal origin. The staining patterns of the microglia cells obtained with hP67.6 antibody were similar to that of the anti-CD68 antibody, confirming that they were indeed microglia cells, which are considered to be macrophages and thus are of mesodermal rather than neuroectodermal origin. The binding specificity of gemtuzumab ozogamicin and the hP67.6 antibody to human normal peripheral blood leukocytes and bone marrow cells was identical.
In vitro cytotoxicity of gemtuzumab ozogamicin in $CD33^+$ and $CD33^-$ cells was investigated in tissue culture assays. The IC_{50} of gemtuzumab ozogamicin for the $CD33^+$ HL-60 cell line was less than 1 pg/ml, while the IC_{50} for the $CD33^-$ Raji cell line was almost [insert value], 100 000-folds higher. Control assays were executed with control antibody conjugates that do not recognise the $CD33^+$ antigen.

The cytotoxic effects of gemtuzumab ozogamicin on HL-60, NOMO-l, NB4, NKM-l cell lines (all $CD33^+$), K562 cells (weakly $CD33^+$), and Daudi cells ($CD33^-$) was investigated. Concentration-dependent and specific cytotoxicity against $CD33^+$ cell lines was observed using flow cytometry to measure cell viability [LC_{50} approximately 0.125 ng/ml of calicheamicin equivalents (cal eq)]. Cells sensitive to gemtuzumab ozogamicin were temporally arrested at the G2/M phase of the cell cycle, except for NKM-1 cells. For the HL-60 cell line, morphological examination and DNA-fragmentation assays indicated that the primary cytotoxic effect of gemtuzumab ozogamicin may be necrotic rather than apoptotic.

The *in vivo* anti-tumour effects of the gemtuzumab ozogamicin were studied in a HL-60 xenograft tumour mouse model. HL-60 xenograft tumours were established by subcutaneous implantation of 8 X 10^6 cells, which had been harvested from ascites. There were 5 nude mice per test group and 10 nude mice in the control group. Tumour mass was determined on a weekly basis. Tumours were staged on average at 8 days post-implantation or when the tumour reached 150 mg. Gemtuzumab ozogamicin was administered as a single dose given intraperitoneally. The data demonstrated a dose-response with an anti-tumour activity at doses between 0.8 and 3.2 mg/m^2 of cal eq. Significant lethality was observed at 3.2 mg/m^2. At the lowest dose of 0.8 mg/m^2, 2 out of 5 mice were tumour free at day 37 post-administration of treatment. Using doses ranging from 0.48 to 2.88 mg/m^2 of calicheamicin equivalents per nude mouse (given on days 7, 11, and 15 post-implantation of tumour?), 5 out of 5 animals were tumour free on day 35. There was >80% inhibition of tumour growth for every group treated with gemtuzumab ozogamicin. Additional experiments with this xenograft mouse model examined the effectiveness of gemtuzumab ozogamicin in comparison with control conjugate non-targeting MOPC-21 antibodies that do not target $CD33^+$ cells specifically but still contain the same calicheamicin derivative. With the corresponding MOPC-21 conjugate, a 20% inhibition of tumour growth was observed.

The effects of gemtuzumab ozogamicin on the colony forming ability of human leukaemia bone marrow samples were investigated. Freshly thawed cell suspensions of bone marrow samples which were known to be capable of forming colonies *in vitro* were exposed to gemtuzumab ozogamicin or control treatments. At 2 ng/mL cal eq, 15% of adult AML patient (n=27) samples had >60% inhibition of colony growth. At 10 ng/mL cal eq the number of samples with >60% inhibition increased to 44%. AML patient samples (n=21) tested at 100 ng/mL cal eq showed high levels of nonspecific inhibition with the non-targeting control and 13 showed a 50% or greater drop in colony growth after incubation with the control conjugate compared to growth with controls at 10 ng/mL cal eq. Results obtained from similar studies using normal bone marrow suggest that normal samples are resistant to gemtuzumab ozogamicin at doses 4-fold higher than those used in the patients.

- Secondary pharmacodynamics

Cytotoxicity studies in normal human megakaryocyte from 6 independent bone marrow donors showed variable results from little or no effect to progressive, cumulative cytotoxicity over 24 hours. Gene expression studies indicated that the observed variability could not be explained by differences in the glutathione pathway or multi-drug resistance genes.

- Safety pharmacology programme

The potential for gemtuzumab ozogamicin to affect vital and other body systems has been investigated.

Cardiovascular system: Three studies were conducted in beagle dogs. In the first study, gemtuzumab ozogamicin administered up to 40 mg protein/m^2 as a single bolus i.v. injection reduced mean arterial blood pressure for 20 minutes (gradually returning toward control values), slightly increased the heart rate but decreased cardiac output. Both P-wave and T-wave amplitudes had a high degree of variability. Vehicle-treated and gemtuzumab ozogamicin-treated animals did not show physiologically significant differences in P-wave and T-wave amplitudes.
In the second study, 13 mg protein/$m^{2\ of}$ gemtuzumab ozogamicin was administered as a 30-minute i.v. infusion, causing no statistical changes in mean arterial blood pressure and cardiac output. However heart rate was significantly increased at all time points starting 15 minutes after infusion. P-wave amplitude was significantly increased at 20 minutes until the end of gemtuzumab ozogamicin infusion (30 minutes) through 90 minutes. T-wave amplitudes were significantly increased at all times starting 15 minutes after infusion.
In the third study, a single dose of 4 mg protein/m^2 of gemtuzumab ozogamicin was administered as a 30-minute i.v. infusion, not causing any change in mean arterial blood pressure, heart rate, and cardiac output, in comparison to vehicle-treated group. P-wave and T-wave amplitudes exhibited considerable variability and were generally not different between vehicle-treated and gemtuzumab ozogamicin-treated dogs. All monitored electrocardiographic parameters were unchanged. Gemtuzumab ozogamicin was without significant physiological effect on overall hemodynamic, cardiac function, or electrocardiographic parameters.

Hepatic function: In rats, i.v. infusion of either vehicle or gemtuzumab ozogamicin at doses of 7.5, 25 and 75 µg calicheamicin eq/kg had no influence on excretion of bromsulphalein sodium compared to the untreated group.

Gastrointestinal (GI) effects: Intestinal motility (mouse *in vivo* study): no significant changes have been observed in urine of levels of protein, sodium, potassium and chloride excretion 5 hours after single i.v. administration of up to 250 µg calicheamicin eq/kg.

Autonomic Nervous System (pig ileum test): gemtuzumab ozogamicin at a concentration up to 0.75 µg calicheamicin eq/ml did not influence spontaneous motility and contractile responses to acetylcholine, histamine, serotonin and barium chloride in isolated guinea pig ileums, suggesting that CMA-676 demonstrates no anti-acetylcholine, anti-histamine, anti-serotonin and Ca^{2+} antagonistic effects.

Effects of vehicle: by using the clinical gemtuzumab ozogamicin sample which contained dextran 40, the effect of gemtuzumab ozogamicin on the volume of urine and urinary electrolytes in rats was not evaluated because of severe hypouresis induced by dextran 40. Hypouresis induced by dextran 40 was not observed in mice.

- Pharmacodynamic drug interactions

Studies on pharmacodynamic drug interactions were not conducted.

Pharmacokinetics

A limited number of pharmacokinetic (PK) studies in animals were performed with gemtuzumab ozogamicin. In light of the absence of cross-reactivity of gemtuzumab ozogamicin (hP67.6 antibody) with the CD33 antigen from other animal species, kinetic studies in animals can only be of limited value, as there will be no binding, specific intracellular uptake, or metabolism of the conjugate that underlies its therapeutic action in humans. This enzyme-linked immunosorbent assay (ELISA) utilizes specific hP67.6 antibody binding to the CD33 antigen. The calibration standard for this ELISA was

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.

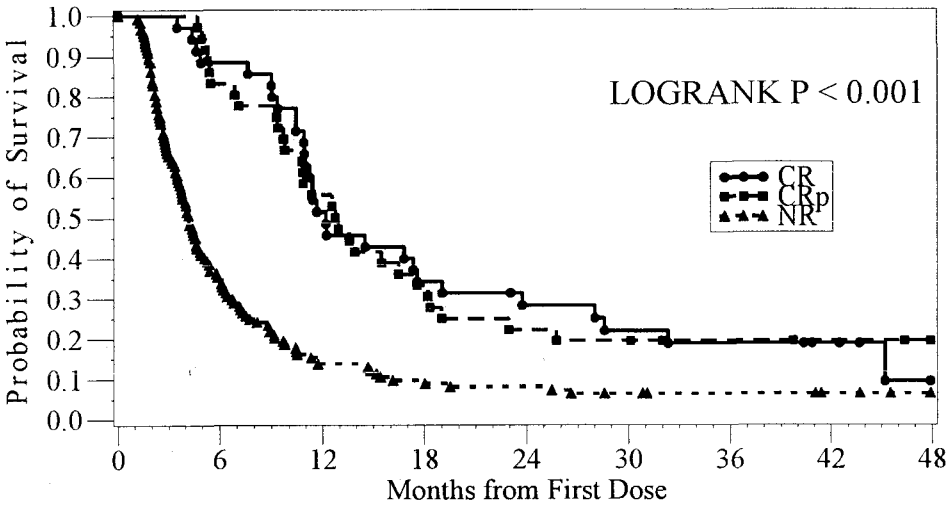
Overall Survival

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

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.

参考資料4

米国マイロターグ発売中止に対する日本臨床腫瘍学会の見解

2010年9月18日

今回の“マイロターグ販売中止と自主的な承認の取下げ”の理由とされた第Ⅲ相臨床試験（SWOG S0106試験）では、未治療の急性骨髄性白血病患者（AML）を対象に、標準的な初回寛解導入療法であるダウノルビシンとシタラビンの併用療法（DA療法）へのマイロターグ（GO）の併用効果、及び、大量シタラビン療法による地固め療法後のGOの追加投与の効果について、いずれも有効性が認められず、逆に有害事象の発現率がGO併用群で有意に高いと報告されています（ASH2009）。これに基づき、ファイザー社が上記の判断をくだしたとされています（ファイザー2010年6月22日プレスリリース）。

日本においては、GOの効能・効果は「再発又は難治性のCD33陽性の急性骨髄性白血病」とされ、しかも「他の抗悪性腫瘍薬と併用しないこと」と明記されております。したがって、対象・用法の異なるSWOG試験の結果が直ちに、日本におけるGO使用に関して、安全性・有効性に関する重大な懸念に結びつくとは考えていません。日本としては、治験や市販後全例調査を通じて独自のデータを集めており、今後とも、添付文書通りの適正な使用を進めていくべきであると考えます。

なお本薬剤の再発例の寛解導入率は内外の報告では30%弱で、市販後の全例調査によると、全396例中完全寛解率は7.8%で奏効率は14.1%でした。急性前骨髄球性白血病に限ると奏功率はかなり高くなりますし、有効薬剤の少ないAML再発例においてその役割は十分あると考えています。英国MRCではAML15試験が進められており、SWOG試験と同様GOランダム化試験が行われていますが、中間解析では予後良好AMLに対する上乗せ効果が報告されています[1]。以上を総合的に判断し、日本での保険適応の範囲の使用であれば発売中止までの措置は必要ないと考えています。

特定非営利活動法人日本臨床腫瘍学会
理事長　田村和夫

【参考】

Larsonら[2]は、1回目の再発、急性骨髄性白血病（AML）277例に、マイロターグを投与。1回の投与で寛解に至らない症例には、2週間間隔で最高3回まで使用した。完全寛解13%、血小板の回復のみ遅れた形態学的寛解は13%で、2つを合わせた全寛解率は26%であった。

日本でも、再発・難治急性骨髄性白血病（再生・難治性AML）の20例に臨床試験が行われ[3,4]、結果は海外の試験とほぼ同様である。完全寛解を5例（25%）、形態学的寛解を1例（5%）に認めた。寛解に至った6例の、寛解導入に要した期間の中央値は62日。本剤の最終投与日から、500/μl以下の期間の中央値は23日、また、血小板数25,000/μl以下の期

間の中央値は28日であった。
一方、日本における市販後の全例調査の結果では、全396例中完全寛解率は7.8%で奏効率は14.1%。有害事象発現率は88.31%、グレード3以上の有害事象が79.5%。VOD/SOS発生率は全体で5.4%（グレード3以上4.4%）、感染症が32.0%（25.9%）、出血が13.2%（8.1%）、注射部位の反応47.3%（24.1%）、肺障害4.0%（3.5%）、腫瘍崩壊症候群3.1%（3.1%）であった（薄井他、日本血液学会2008）。
さらに、日本において、再発・難治性AML患者19人に対して、MRC-AML15と同様の低用量GOと標準的化学療法の併用療法の第I相臨床試験が行われ、安全性が報告された（薄井他、日本臨床血液学会2010）。

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