

**Mylotarg  
NDA 21-174**

**ODAC Briefing Document  
October 5, 2005**

**MYLOTARG<sup>®</sup> (GEMTUZUMAB OZOGAMICIN FOR INJECTION)  
NDA NO. 21-174**

**BRIEFING DOCUMENT  
FOR THE  
ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC) MEETING  
NOVEMBER 8, 2005**

**Holiday Inn Gaithersburg  
2 Montgomery Village Avenue  
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**AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION**

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**APPENDIX 1: *Mylotarg® (gemtuzumab ozogamicin for Injection) product labeling***

**ONCOLOGIC DRUGS ADVISORY COMMITTEE MEETING  
BRIEFING DOCUMENT FOR MYLOTARG<sup>®</sup>(GEMTUZUMAB OZOGAMICIN FOR  
INJECTION)  
NDA NO. 21-174**

**1.0 SUMMARY**

The Division of Oncology Drug Products sent notice (dated July 8, 2005) to pharmaceutical companies with drugs approved under 21 CFR Part 314.500 (Subpart H, accelerated approval regulations), inviting participation in an open session at the November 8, 2005 meeting of the Oncologic Drugs Advisory Committee (ODAC). Wyeth was invited to present an update on the Subpart H clinical phase 4 commitments for Mylotarg.

Mylotarg was approved in May 2000, as a single agent for the treatment of 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 post approval commitment specified a randomized controlled trial in combination therapy and to conduct the appropriate phase 1 trials to ensure the safety of the dose for combination therapy. In August 2000, shortly after NDA approval, Wyeth initiated in parallel, the two prerequisite phase 1/2 studies in combination with standard chemotherapy and these studies were completed in April 2003. On the basis of the results of these pilot studies, the post approval commitment study was designed. This confirmatory study was discussed and agreed with FDA through the Special Protocol Assessment process. In June 2003, Wyeth obtained concurrence from FDA that the phase 3 protocol design (SWOG S0106) for patients with *de novo* CD33 positive AML in combination therapy, would fulfill the post approval commitment outlined in the NDA approval letter and could support two indications, induction therapy and post-consolidation therapy with Mylotarg. The final protocol was filed in November 2003. Due to the orphan nature of AML, this study was developed in collaboration with the Southwest Oncology Group (SWOG) and is being conducted by SWOG under their IND, on behalf of Wyeth.

The post approval commitment study was initiated in 2004 with the first patient enrolled in August 2004. Enrollment is in progress with an improved trend in the number of patients accrued per month over the last few months. Wyeth and SWOG are working to enhance the accrual rates. Additional details regarding ongoing activities will be presented at the upcoming ODAC meeting on November 8, 2005.

This document provides background information on the Subpart H accelerated approval of Mylotarg, including recommendations for use, safety information and information on AML and its treatment options. A review of Wyeth's post-marketing clinical commitments and their status since the last ODAC meeting in March 2003 is provided in the following sections. At the 2003 ODAC meeting, the post approval commitments under Subpart H studies which included the two phase 1/2 studies (Protocols 0903B1-205 and 0903B1-206) and the confirmatory study (Protocol

S0106) were presented, as well as a post approval observational safety study (Protocol 0903X-100847) in usual care.

## **2.0 BACKGROUND**

On October 29, 1999, Wyeth submitted a new drug application (NDA) for Mylotarg® (gemtuzumab ozogamicin for Injection). Mylotarg was also granted orphan drug status on November 24, 1999. The Food and Drug Administration (FDA) completed the review of the application according to the regulations for accelerated approval, and concluded that adequate information was presented to approve Mylotarg for the treatment of patients with CD33 positive acute myeloid leukemia in first relapse who are 60 years of age or older and who are not considered candidates for other cytotoxic chemotherapy. This application was approved on May 17, 2000 under 21 CFR Subpart H, a program described in the regulations as intending to make promising products for life threatening diseases available to the public on the basis of preliminary evidence of safety and efficacy.<sup>1</sup>

Mylotarg was approved on the basis that the product has an effect on a surrogate endpoint, Overall Response Rate (ORR), reasonably likely to predict a clinical benefit. Response rates were categorized by Wyeth and FDA as Complete Remission (CR) and remission with incomplete platelet recovery (CR<sub>p</sub>). The original NDA contained analysis of three phase 2 studies of patients with relapsed AML. There were no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival, compared to any other treatment.

Subsequent to the NDA approval, the International Working Group (IWG) on AML endpoints established comparable standard criteria for response in 2003<sup>2</sup>. Wyeth's response definitions (CR and CR<sub>p</sub>) are similar to those established by the IWG.

## **3.0 ACUTE MYELOID LEUKEMIA**

AML is the most common type of acute leukemia in adults. The American Cancer Society estimated that 11,960 new cases of AML and 9,000 deaths from AML would occur in the United States in 2005.<sup>3</sup> It is estimated that Mylotarg could potentially be used to treat approximately 2,100 patients per year in the USA within its recommended indication. Slightly more than one half of all patients with AML are 60 years of age or older.

Untreated AML is a rapidly progressing fatal disease, with a median survival time of less than 3 months. With standard treatments for patients with *de novo* AML, a high rate of first remission is achieved, but approximately 75% of patients with first remission ultimately relapse. The majority of relapses occur within 2 years after remission is attained. The American Cancer Society reported 5-year survival rates of 18.7% for patients with AML. Patients 60 years of age

and older have a lower remission rate, a reduced probability of remaining in remission, and have a lower cure rate than younger patients.

Patients with relapsed AML have a particularly poor prognosis. Significant morbidity and mortality are associated with current therapies for patients with relapsed AML, particularly for patients 60 years of age and older, patients with a variety of cytogenetic abnormalities, patients with relatively short durations of first remission (i.e. < 12 months) and for patients with co-morbid conditions<sup>4,5,6,7,8</sup>. While numerous therapies and dosage regimens have been investigated in an attempt to improve remission and survival rates in patients with relapsed AML, none have emerged as a standard of care. Mylotarg was the first agent specifically approved for the treatment of patients with relapsed AML.

#### **4.0 THERAPEUTIC OPTIONS**

Most patients diagnosed with AML receive induction therapy to attain remission and post-remission therapy to maintain remission.<sup>9</sup> Approximately 50% to 70% of adults with AML attain complete remission (CR) following treatment.<sup>10,11</sup> About 25% of these patients survive 3 or more years.<sup>12</sup> Unfortunately, more than 75% of patients relapse.

Induction chemotherapy with cytarabine and an anthracycline has been a standard treatment of newly diagnosed AML for the past 25+ years. Complete remission can be achieved in 50% to 70% of adult patients less than 60 years old with *de novo* AML when treated with cytarabine and an anthracycline, depending on the prognostic factors in the population treated. However, only 20% of patients who achieve a remission with induction chemotherapy and consolidation therapy have prolonged leukemia-free survival. The induction CR rates for patients over the age of 60 are generally lower due to many factors including a higher incidence of poor prognostic cytogenetic abnormalities and higher mortality from intensive therapy. Several non-transplant strategies have been employed to intensify the induction regimen with the hope of improving the remission rate, duration of remission, and survival. Therapy with high dose cytarabine as post-remission therapy for patients with *de novo* AML in remission has improved the duration of the remission.

Induction therapy typically consists of 7 days of cytarabine (ara-C) plus 3 days of an anthracycline such as idarubicin or daunorubicin and/or an anthracenedione such as mitoxantrone.<sup>9</sup> In large randomized clinical trials, these regimens have been shown to achieve CR in 52% to 72% of patients.<sup>10</sup> In a report by Bennett and colleagues (1997), 62% of patients experienced CR, and the median 5-year disease-free survival rate was 22%.<sup>13</sup>

The most common toxicity associated with induction regimens is myelosuppression. Thrombocytopenia frequently occurs and, if severe, can lead to life threatening hemorrhage. Neutropenia, particularly when associated with breakdown of the skin or mucous membranes,

e.g., mucositis, can rapidly lead to fever, severe infections and often progress to septic shock and death. Cardiotoxicity is dose cumulative and a common adverse effect of the anthracyclines.<sup>14,15,16,17,18,19,20</sup>

Patients must be closely monitored for signs of bleeding and infection to receive appropriate rapid supportive care including prophylactic and specific broad-spectrum antimicrobial therapy at the first signs of a possible infection and hematological support, e.g., platelet transfusions, to avoid life threatening hemorrhage, the two major causes of death in AML patients.<sup>10</sup> Red blood cell transfusions are indicated prior to when the patient is in jeopardy of having inadequate tissue oxygenation.<sup>21</sup>

Disease-free survival and 5-year survival rates have been shown to increase following post-remission consolidation and intensification therapy.<sup>13,22</sup> Hematopoietic stem cell transplantation with a variety of ablative and non-ablative regimens have been used successfully as post-remission therapy for patients with AML.<sup>23,24,25,26,27</sup>

Relapsed AML is associated with poor probability of attaining second remission or substantial disease-free and overall survival.<sup>9</sup> Usually, the outcome is better for younger, healthier patients and those with long initial remissions. For patients 60 years of age and older, the probability of attaining a second remission is approximately 25%, whereas in younger patients it may be somewhat higher.<sup>9</sup>

There is no standard treatment for patients with relapsed AML. If relapse occurs  $\geq$  18-24 months after attaining a first remission, re-administration of the original remission-induction regimen may be effective.<sup>6</sup> Regimens consisting of high-dose cytosine arabinoside alone or in combination with agents such as mitoxantrone have been investigated. Some patients with relapsed AML respond to allogeneic bone marrow transplant (BMT) or autologous BMT with or without purging.<sup>12,23,28,29</sup>

Monoclonal antibodies (MoAbs) that target specific antigens can be used to deliver cytotoxic agents to specific cells within the body. Despite the simplicity of this concept, the actual development of therapeutic agents has been complicated by a number of technical difficulties, including the selection of an appropriate target antigen.<sup>30</sup> CD33 is expressed on AML leukemic blasts in  $>$  80% of patients. This epitope is not expressed on the hematopoietic progenitor stem cell.<sup>31,32</sup> Antibody-targeted chemotherapy consists of a MoAb conjugated to a cytotoxin or a chemotherapeutic agent. To exert their effects, MoAbs conjugated to potent cytotoxic agents must be internalized by the cell to disrupt critical intracellular processes and induce cell death.<sup>30</sup> The "linker" between the MoAb and the toxic agent is a key element of this type of therapy. The toxic agent must remain bound to the monoclonal antibody via the linker while in the serum and be efficiently released within the target cell without significant alteration in its activity.<sup>33</sup> Mylotarg is one example of this type of conjugate and is discussed in more detail in the following section.

## **5.0 MYLOTARG (GEMTUZUMAB OZOGAMICIN)**

Mylotarg is the first antibody targeted chemotherapy agent approved by the FDA, and is composed of a humanized anti-CD33 antibody [hp67.6] linked to a potent anti-tumor antibiotic, calicheamicin<sup>34</sup>. It is indicated for the treatment of patients with CD33 positive acute myeloid leukemia in first relapse who are 60 years of age or older and who are not candidates for other cytotoxic chemotherapy.

Mylotarg as a single agent demonstrated efficacy similar to that reported in the literature for conventional AML treatment in relapsed patient populations as measured by remission rate. Rates of myelosuppression, severe bleeding, and liver enzyme abnormalities were similar to or perhaps lower than the rates reported for other therapies. The incidence of veno-occlusive disease (VOD) was 5% overall, 1% in patients that did not have associated hematopoietic stem-cell transplant (HSCT) and 17 % in patients who had an associated HSCT. This syndrome is usually observed following conditioning for HSCT.

In the Mylotarg single agent studies, a lower rate of severe infections, and subsequently a lower total duration of hospitalization was observed as compared to other treatment regimens used in similar patient populations. Patients treated with Mylotarg experienced a low rate of severe mucositis during neutropenia and may explain the lower observed rate of infections than expected. Additionally, there was no alopecia reported.

Patients 60 years of age and older with AML are a distinct subset of AML patients; they have lower response rates to antileukemic therapies and decreased survival rates. In Mylotarg phase 2 studies, the median age was 60 years. The overall response rate (OR) rate in all patients was 26%, in patients < 60 years old the OR rate was 28%, and in patients ≥ 60 years old the OR rate was 24%.

Similar to other antibody-based therapies, a mild infusion-related symptom complex of fever, chills and, less frequently, hypotension and dyspnea, associated with Mylotarg administration was observed in most patients. An acute infusion-related symptom complex occurred within 24 hours after administration of Mylotarg and was usually self-limiting. Also, no patients developed an immune response to Mylotarg in the phase 2 studies.

Hepatotoxicity, including severe hepatic 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 HSCT. 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. Death from liver failure and from VOD has been reported in patients who received Mylotarg. In April 2001, Wyeth, in conjunction with FDA, agreed to develop a

voluntary patient safety registry and details of the progress of this study is provided in Section 8.0.

The overall benefit/risk of Mylotarg for treatment of relapsed AML is positive. The efficacy of Mylotarg, when administered in 2 doses of 9 mg/m<sup>2</sup> IV with a 14-day interval between doses, was similar to other AML therapy in similar patient populations.

## **6.0 POST-MARKETING CLINICAL COMMITMENT**

A description of the commitment as stated in the FDA Approval Letter (17 May 2000) is provided below:

“A randomized controlled trial of gemtuzumab ozogamicin, daunorubicin and cytarabine versus daunorubicin and cytarabine as induction therapy in patients with de novo CD33-positive acute myeloid leukemia. This trial should be designed to demonstrate superior survival in the three-drug (gemtuzumab ozogamicin containing) group. Response rate results can be used as supportive evidence; responses should be defined as CR’s or CRp’s of at least 4 weeks duration. If the three-drug regimen cannot be designed with acceptable toxicity, a randomized controlled trial designed to show that survival in patients treated with gemtuzumab ozogamicin and cytarabine is not inferior to survival in patients given daunorubicin and cytarabine should be initiated following discussion with the division. Again, the definition of the supportive secondary end point, response (CR and CRp), should include a pre-specified minimum duration of response of 4 weeks.

For either trial it will be necessary to:

- a. Clarify the purpose and the number of interim analyses planned, adjusting type I error as necessary. An independent, expert data monitoring committee will review bone marrow results, conduct the interim analysis, and make recommendations regarding continuation of the study. Responses should be determined by an independent pathologist blinded to the treatment arm.
- b. Pre-specify subgroups and covariates that are likely to be used in the analyses. The relationship of CD33 quantitative expression to response should be examined.
- c. Perform a thorough evaluation of toxicity, both hematologic and non-hematologic, in patients undergoing subsequent post-remission therapy as hematopoietic stem cell transplantation or high dose cytarabine, as well as in patients who receive no further therapy.
- d. Perform long-term follow-up for relapse and survival in patients following post-remission therapy, as well as for patients who receive no further therapy.
- e. Perform the appropriate phase 1 trials to ensure that toxicities observed with the dose combinations in the above trials are acceptable; and to identify any potentially significant pharmacokinetic drug-drug interactions.”

## **6.1 Phase I/II Combination Studies**

Following approval of Mylotarg as a single agent, phase 1/2 dose-ranging studies were required prior to the initiation of the pivotal study to determine dosing of Mylotarg in combination with other standard of care chemotherapy agents. The following summary provides an update of the dose-ranging studies which have now been completed.

**Protocol No. 0903B1-206-US:** *A Dose Ranging Study of the Safety and Efficacy of Gemtuzamab Ozogamicin (GO) given in Combination with Cytarabine and Daunorubicin in Relapsed or Refractory Patients and in Younger De Novo Patients with Acute Myeloid Leukemia.*

The purpose of the pilot study is to evaluate the safety and efficacy of administering Mylotarg concurrently with an anthracycline and cytarabine in AML patients. The goal of the study was to define a combination treatment arm utilizing Mylotarg, an anthracycline, and cytarabine, which will be compared to an anthracycline and cytarabine arm in a randomized phase 3 trial of *de novo* AML.

This study is now completed and enrolled 71 patients. Of the 71 patients, 53 patients received the day 4 dose of Mylotarg and were included in the efficacy analysis. Forty-one (41) of 53 (77%) patients had CR and 1 patient had CRp, giving an overall remission (OR) rate of 79%. Twenty-seven (27) of the 53 patients were still alive at 1 year. In general, the safety profile observed in this study appears to be similar to Mylotarg when used as a single agent.

**Protocol No. 0903B1-205-US:** *A Dose Ranging Study of the Safety and Efficacy of Gemtuzamab Ozogamicin (GO) given in Combination with Cytarabine in Relapsed or Refractory Patients and in Older De Novo Patients with Acute Myeloid Leukemia.*

In an attempt to improve the survival of older patients with AML, this trial was designed to substitute Mylotarg for standard anthracycline dosing in remission induction therapy for *de novo* AML. As toxicity of therapy is a major barrier to treating older AML patients, the proposed study was a pilot trial to evaluate the safety and efficacy of administering Mylotarg with continuous infusion cytarabine in AML patients. The eventual goal of the study was to define a combination treatment arm that could be compared to cytarabine/anthracycline therapy in a randomized trial of AML in older patients.

This study is now completed and 38 patients were enrolled. Efficacy was evaluated for 17 patients in phase 2 and 4 *de novo* patients in phase 1 who were treated at the selected dose. Of the 21 patients evaluated for efficacy, 9 (43%) had CR and 1 (5%) had CRp. The overall remission (OR) rate was 48%. In general, the safety profile observed in this study appears to be similar to Mylotarg when used as a single agent.

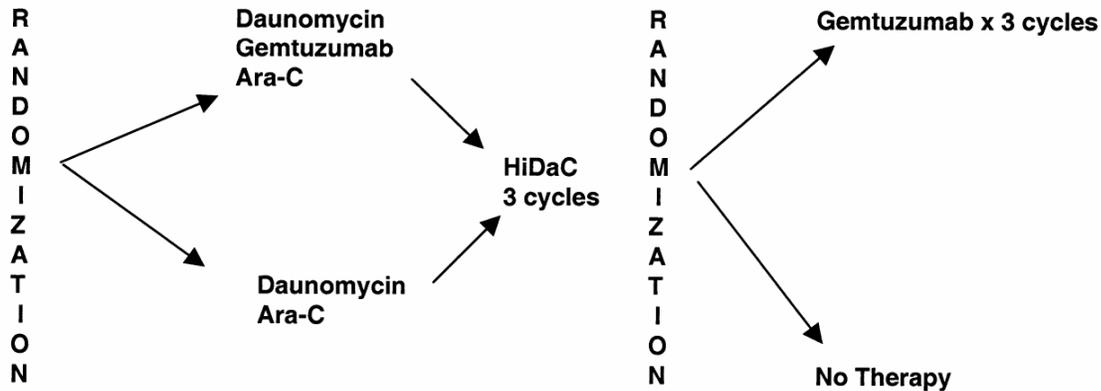
**6.2 Status of the Subpart H Phase 4 Clinical Commitment**

Based on the findings from studies 205 and 206 referenced previously, Wyeth, in collaboration with the Southwest Oncology Group, designed the following study:

**Protocol No. S0106:** *A Phase III Study of the Addition of Gemtuzumab Ozogamicin (Mylotarg®) Induction Therapy Versus Standard Induction with Daunomycin and Cytosine Arabinoside Followed by Consolidation and Subsequent Randomization to Post-Consolidation Therapy with Gemtuzumab Ozogamicin (Mylotarg®) or No Additional Therapy for Patients Under Age 56 with Previously Untreated de novo Acute Myeloid Leukemia (AML)*

This study will determine if *de novo* AML patients (excluding acute promyelocytic leukemia [PML - M3] AML patients) will achieve a significantly increased induction response rate when Mylotarg is added to (a) standard induction therapy, (b) added as post-consolidation therapy versus no post-consolidation therapy or (c) both. In the first phase of this study, patients will be randomized to receive either standard induction therapy utilizing 7 days of cytosine arabinoside and 3 days of daunomycin (7+3), or the experimental arm with 7+3+Mylotarg on day four. All patients with acute myeloid leukemia regardless of CD-33 expression are eligible for randomization. In the second phase of the study, complete responders will receive 3 cycles of high dose cytosine arabinoside as consolidation. After completion of consolidation, remission patients will be randomized to receive post-consolidation therapy with 3 cycles Mylotarg or no additional therapy.

**Schema**



Patients must have a morphologically confirmed diagnosis of AML with FAB classification other than M3, based on bone marrow aspiration and biopsy performed within 14 days prior to registration. Patients with M3 AML or blastic transformation of chronic myelogenous leukemia

are not eligible. Patients with a preexisting hematologic disorder evolving to AML such as myelodysplasia or secondary leukemia are not eligible. Patients must not have received systemic chemotherapy or more than one dose of intrathecal chemotherapy for acute leukemia. Administration of hydroxyurea to control high cell counts prior to registration is permitted. Patients must have reached their 18th birthday but not reached their 56th birthday and must have a Zubrod performance status in 0-3. Patients must have normal hepatic and left ventricular function. Patients with unstable cardiac arrhythmias or un-stable angina are not eligible.

The objectives of this study are as follows:

- To compare the disease-free survival (DFS) of patients under age 56 with previously untreated, *de novo*, non-M3, AML who receive Mylotarg as post-consolidation therapy versus patients who receive no post-consolidation therapy.
- To compare the complete remission rate achieved by the addition of Mylotarg to standard induction chemotherapy to that achieved with standard induction chemotherapy in patients under the age of 56 with previously untreated, *de novo*, non-M3 AML. The durability of the responses will also be measured.
- To estimate the frequency and severity of toxicities of the addition of Mylotarg to induction therapy and post-consolidation therapy.
- To evaluate the prognostic significance of CD33 expression on the response rate of patients who receive Mylotarg.
- To evaluate the prognostic significance of FLT3 mutation prior to therapy, and of minimal residual disease in remission specimens collected before and after consolidation therapy and after post-consolidation therapy with Mylotarg.
- To evaluate the prognostic significance of the flow cytometric detection of minimal residual disease in specimens collected before and after consolidation therapy and after post-consolidation therapy with Mylotarg.

Safety and efficacy monitoring includes routine patient monitoring conducted at the study sites, and a Data and Safety Monitoring Committee, who will oversee the conduct of this study. This committee will be responsible for decision regarding the termination and/or early reporting of the results of this study.

The aforementioned study protocol was reviewed with the FDA via Special Protocol Assessment submitted in December 2002. FDA comments were received February 2003 and a Type B meeting was held between FDA, Wyeth and representatives of SWOG in June 2003. FDA

concluded that the design of the SWOG study fulfills the requirements for the Subpart H commitment for Mylotarg (NDA 21-174). The final study protocol, which was available November in 2003, is being conducted by SWOG under their IND, on behalf of Wyeth. This study was activated in 2004 with the first patient enrolled in August 2004. There are 225 sites in the United States planned for inclusion in the study, of which 196 sites have received IRB approval. The current accrual is 52 patients and the enrollment rate is increasing. The accrual goal is 684 patients over 4.5 years with a 3 years follow-up period from the time of the last enrolled patient. The estimated timeline for the study completion is in 2012, which includes the 3-year follow-up period. The study results are anticipated to be submitted to the FDA on or before 2013; multiple interim analyses are planned during both the induction and post-consolidation phases of this study.

## **7.0 PROSPECTIVE OBSERVATIONAL STUDY**

In addition to the previously mentioned confirmatory study (S0106) under the Subpart H clinical commitment, the status of a Wyeth sponsored Mylotarg prospective observational safety study, is summarized below. The status of the prospective observational safety study was previously presented at the ODAC meeting in March 2003. This voluntary safety patient registry study was developed in conjunction with FDA after the approval of Mylotarg.

**Protocol No. 0903X-100847:** *Prospective Observational Study of Mylotarg® (gemtuzumab ozogamicin) in Usual Care.*

Mylotarg has a boxed warning on the label (see attached prescribing information) addressing hypersensitivity reactions including anaphylaxis, infusion reaction, pulmonary events, and hepatotoxicity including VOD.

On April 12, 2001, Wyeth, in conjunction with FDA, agreed to develop a voluntary patient safety registry. All centers that agree to participate in the observational study are required to seek permission from every patient at their institution who is going to be given Mylotarg, regardless of whether it is given on or off-label or if the patient is in another study or not. The study design is that of a prospective observational registry conducted under conditions of routine clinical practice by oncologists/hematologists administering Mylotarg. The primary objectives of this registry are to estimate the incidence rate of hepatic VOD among patients treated with Mylotarg and to identify risk factors associated with the development of VOD after Mylotarg treatment. Secondary objectives of the registry are to collect and report all serious adverse events, and non-serious adverse events of special interest comprised of hepatic, hypersensitivity, infusion-related, pulmonary, and renal events, and to collect information on Mylotarg use in various practice settings.

The observational study was initiated in July 2001 and has enrolled 454 patients at 59 sites throughout the United States. The target enrollment for this study is approximately 500 patients. An interim analysis has been conducted and the results submitted to FDA in March 2005. To date, the observations indicate that there has not been a significant change in the safety profile of Mylotarg. We anticipate study enrollment to be completed in 2006, followed by a 6- month follow-up period and the study results will be submitted to the FDA thereafter.

## **8.0 CONCLUSION**

Wyeth continues to actively work towards meeting our obligations for Mylotarg in a timely manner. Since Mylotarg was initially approved as a single agent treatment, it was necessary for Wyeth to conduct two studies using Mylotarg in combination with other chemotherapy agents prior to the start of the actual post-marketing clinical commitment study. These phase 1/2 dose-ranging studies were a required prerequisite to establish a safe dose of Mylotarg when used in combination with other agents. On the basis of results from the phase 1/2, a phase 3 study protocol was designed to meet our Subpart H phase 4 clinical commitment study. In addition to addressing the specific question posed in our post approval commitment, i.e., the impact of Mylotarg on induction in patients with *de novo* CD33-positive AML, it was also designed to answer a second important clinical question, the effect of Mylotarg as post-consolidation therapy. This study is being conducted in collaboration with SWOG. The phase 3 study is in progress, with the majority of study sites with IRB approval and the rate of enrollment is increasing.

Wyeth and SWOG have been actively working together and are implementing several additional measures to further enhance study accrual. Enrollment in the phase 3 study is discussed on an ongoing basis between Wyeth and SWOG. Several major institutions that have not been able to participate earlier in the study are in the process of submitting for IRB approval and activating their centers to participate in this study. Other measures undertaken include increased awareness of the study. Activities are ongoing to engage patients and sites, including the participation of other cooperative groups and these will be presented at the ODAC Committee on November 8, 2005. Wyeth fully recognizes its responsibility for meeting this post approval commitment in a timely manner and continues to diligently monitor the study's progress.

Wyeth also continues to closely monitor for any safety issues that may be associated with Mylotarg through the Prospective Observational Study, clinical study analysis, and routine post-marketing surveillance. An interim analysis report on the Prospective Observational Study was submitted to FDA in March 2005.

The approval under Subpart H has allowed Mylotarg to be made available as a treatment option to doctors with patients who are  $\geq 60$  years of age and have AML in first relapse. Prior to the approval of Mylotarg, there were no approved options for these patients. With Mylotarg having

demonstrated a clinically important positive benefit in its target population, the approval of Mylotarg has provided a treatment option of value to the medical community.

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