CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

NDA or BLA Number	BLA761060
Link to EDR	\\CDSESUB1\evsprod\BLA761060
Submission Date	November 2, 2016
Submission Type	Standard BLA
Brand Name	Mylotarg
Generic Name	Gemtuzumab Ozogamicin
Dosage Form and Strength	Vial containing 5 mg of gemtuzumab ozogamicin to be reconstituted with 5 mL of sterile water for injection
Route of Administration	intravenous
Proposed Indication	• Combination therapy with daunorubicin (DNR) and cytarabine (AraC) for the treatment of adult patients with previously untreated, de novo acute myeloid leukemia (AML) • Treatment of patients with acute myeloid leukemia in first relapse who are 60 years of age or older and who are not considered candidates for other cytotoxic chemotherapy
Applicant	Pfizer
Associated INDs	IND04663, NDA021174
OCP Review Team	Jee Eun Lee, Ph.D., Jiang Liu, Ph.D., Christy John, Ph.D., Gene Williams, Ph.D., Nam Atiqur Rahman, Ph.D., Yaning Wang, Ph.D.

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1 EXECUTIVE SUMMARY

Gemtuzumab ozogamicin (GO; Mylotarg®) is an antibody-drug conjugate (ADC) composed of CD33-directed monoclonal antibody (hP67.6; recombinant humanized immunoglobulin (Ig) G4, kappa antibody) that is covalently linked to the cytotoxic agent N-acetyl-gamma calicheamicin (NAc-calicheamicin). GO was granted an accelerated approval on May 17, 2000 as a monotherapy with dose of 9 mg/m^2 with the treatment course of 2 doses total, administered 14 days apart. The approved indication is 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 cytotoxic chemotherapy. During the post-marketing period, incidents of fatal hepatotoxicity and veno-occlusive disease (VOD) were found to be higher than those observed during the registration trial. Thus, boxed warnings highlighting risk of hepatotoxicity including severe hepatic VOD in association with the use of GO were added in the labeling. To fulfill a PMR to confirm the clinical benefit of GO, Study SWOG S0106 was conducted to compare the efficacy of GO + daunorubicin (DNR)/cytarabine (AraC) with the efficacy of DNR/AraC. The GO dose of 6 mg/m^2 was used in the randomized trial in de novo patients ≤60 years of age. The study results showed that GO did not add to the efficacy of the backbone therapy but showed higher induction toxicity with GO. The applicant (Wyeth) withdrew Mylotarg® from the market in November 2011.

The Applicant submitted a new BLA with data obtained from a randomized trial (ALFA-701) with a fractionated lower doses of 3 mg/m^2 (on Days 1, 4, and 7) of GO in combination with DNR/AraC in de novo AML patients (N=271) aged 50 - 70 years. The results from ALFA-701 showed a significantly better event free survival (EFS) benefit and numerically better overall survival (OS) of addition of GO to DNR/AraC, but no significant difference between the arms in 30-day mortality (See section 3.1). However, PK measurements were not obtained from study ALFA-701. Along with the submission, the Applicant also submitted the request to re-approve the original indication for relapsed AML with originally approved dose of 9 mg/m^2 as a monotherapy with no additional data.

(b) (4)

Based on data from several clinical trials from literature (see section 3.3.2), exposure-response relationships for efficacy/safety, CD33 target occupancy, and better benefit/risk profile of the fractionated dose, a fractionated dose of 3 mg/m^2 is supported as the monotherapy for relapsed AML (see section 2.2.1).

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed this BLA and found the BLA is approvable from a clinical pharmacology perspective. The recommended GO dose is 3 mg/m^2 (on Days 1, 4, and 7) in combination with DNR/AraC for de novo AML and as a single agent for relapsed AML.

1.2 Post-Marketing Requirements and Commitments

A PMC study to evaluate the efficacy, safety, and PK of 3 mg/m^2 (on Days 1, 4, and 7) regimen as a monotherapy is recommended.

2 SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics and Pharmacodynamics

Gemtuzumab ozogamicin (GO) is an antibody-drug conjugate (ADC) composed of CD33-directed monoclonal antibody (mAb; recombinant humanized immunoglobulin [Ig] G4, kappa antibody). Pharmacokinetics of antibody (hP67.6), total calicheamicin was characterized with data obtained from earlier Phase 1 studies (Study 101 and Study 102) where doses ranging from 0.25 mg/m^2 to 9 mg/m^2 were administered. Half-life of hP67.6 was approximately 31 hours following the first dose of 9 mg/m^2 and 45 hours after the second dose of 9 mg/m^2. PK of unconjugated calicheamicin was not well characterized since plasma concentrations of unconjugated calicheamicin were low and could be measured only for a short time after the end of infusion. Tmax was 2 hours post-dose for all analytes, which is the end of infusion. Half-life of total calicheamicin was ~41 hours following the first dose of 9 mg/m^2 and 59 hours after the second dose of 9 mg/m^2. Inter-subject variability was very large: %CV was 62% and 136% for Cmax and AUC of hP67.6, respectively, at the 9 mg/m^2 dose level. Dose-normalized exposure appeared to increase as dose increased.

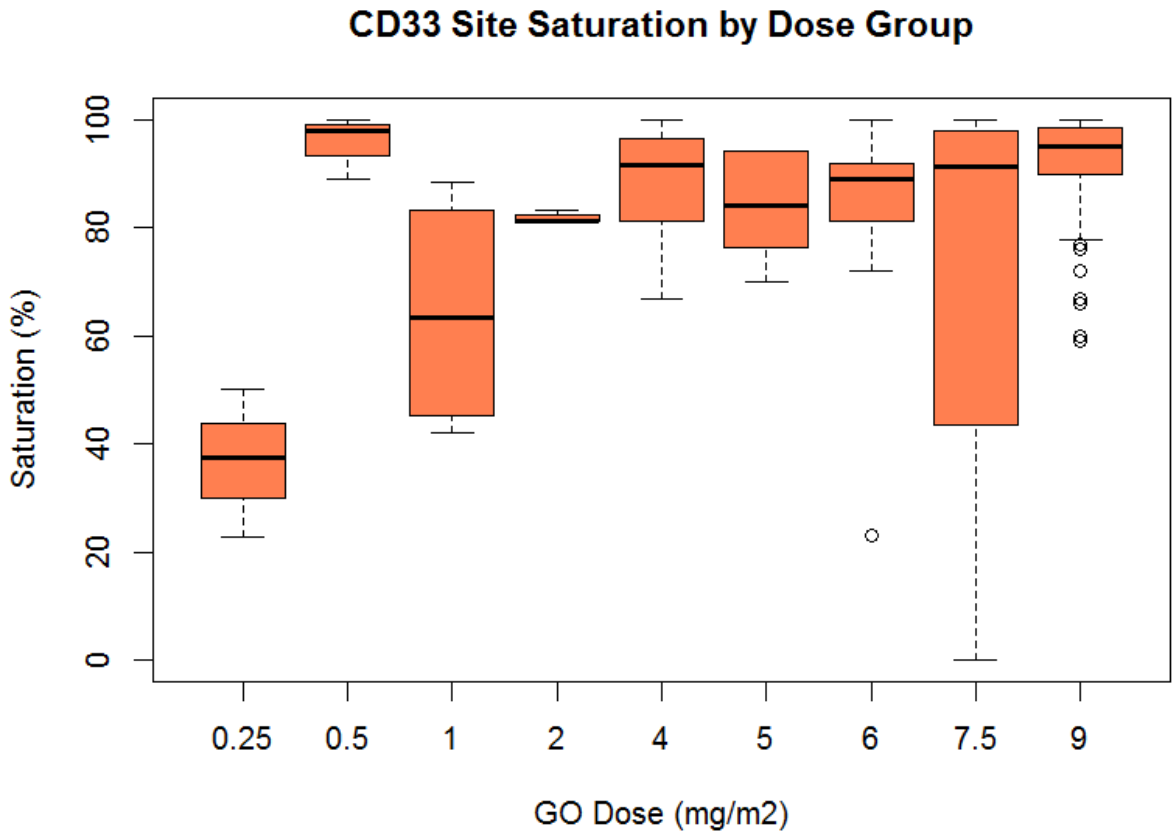
Population PK analyses found that the clearance (CL) value of hP67.6 from plasma was 0.35 L/h after the first dose and 0.15 L/h after the second dose, a decrease of roughly 60%. The terminal plasma half-life ($t_{½}$) for hP67.6 was estimated longer than that from Phase 1 studies: 62 hours after the first dose and 90 hours after the second dose.

Plasma protein binding was high in human plasma (unbound fraction = 0.028) and calicheamicin is a substrate of P-gp. Biotransformation of NAc-gamma-calicheamicin occurs primarily via non-enzymatic reduction.

Saturation of a high percentage of CD33 antigens is believed to be required for maximum delivery of calicheamicin to leukemic blast cells. The relationship between dose and CD 33 site saturation is shown in Figure 1. It appears that CD 33 antigen is saturated with GO dose of 2 mg/m^2 and above. This is in agreement with the sponsor's conclusion from its estimated ED50, ED90 and ED95 which

were 0.2 mg/m^2, 1.6 mg/m^2 and 3.3 mg/m^2, respectively.

Figure 1: CD33 Site Saturation Following Single Dose of GO at Doses Ranging from 0.25 mg/m^2 to 9 mg/m^2



(Reviewer's Analysis)

Because PK/PD following the proposed dose of 3 mg/m^2 has never been evaluated, it should be characterized in the recommended PMC study where efficacy and safety of fractionated dosing regimen of 3 mg/m^2 will be evaluated.

2.2 Dosing

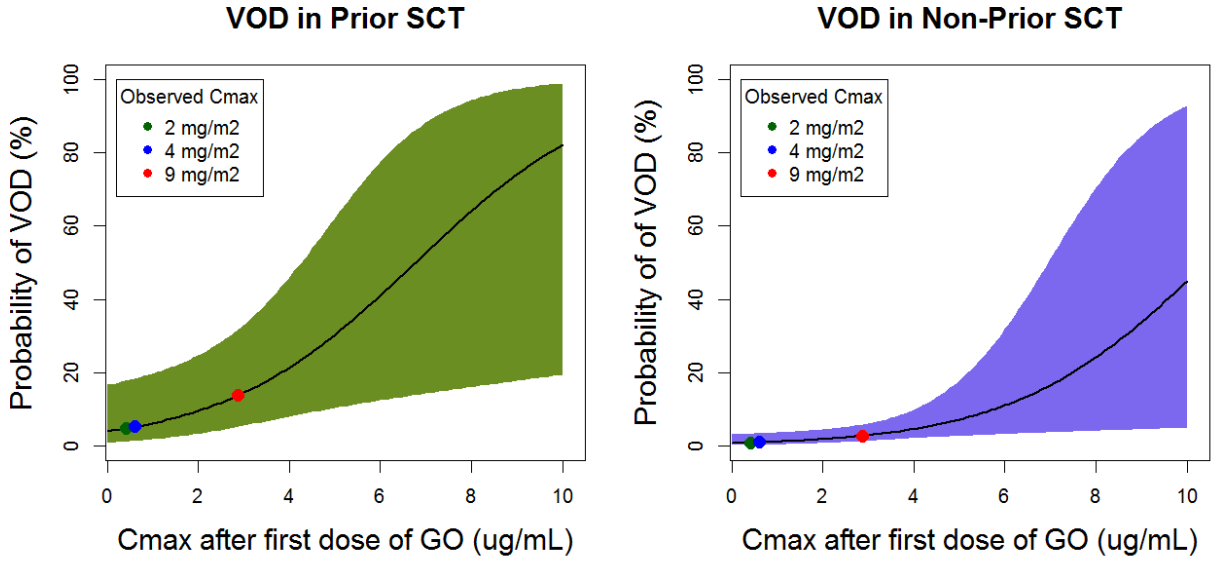
2.2.1 General dosing

The results from Study ALFA-0701 indicate the studied dose of GO (fractionated dosing of 3 mg/m^2 on Days 1, 4, 7 for induction) provides improved clinical benefit for event-free survival (EFS). The estimated median time [95% CI] for EFS in DA+ GO arm vs. DA arm was 39.8 [30.2, 49.3] months vs. 13.6 [5.8, 24.8] months, and the hazard ratio [95% CI] was 0.56 [0.42, 0.76].

Higher rates of hemorrhage (8% vs. 4%) and liver toxicity (4% vs. <1%) were reported in patients with GO+DA vs. DA alone. 30-day mortality was similar between GO+DA arm (3.8%) and DA alone arm (2.2%). VOD was greater in GO+DA (3% vs. 0). According to meta-analyses conducted by the clinical/statistical team, early mortality and VOD associated with Mylotarg generally appear to be reduced with fractionated dosing of 3 mg/m^2 compared to 9 mg/m^2. Thus exposure-response analyses for efficacy and safety were performed to evaluate the benefit of fractionated dosing regimen using data originally submitted for GO single agent of 9 mg/m^2 dose.

As shown in **Error! Reference source not found.**, the risk for VOD increases as Cmax after first dose of GO increases. The increase in VOD is more prominent in patients with prior stem cell transplantation. After adjusting for prior stem cell transplantation, the effect of Cmax on the risk of VOD was still significant (p=0.0339).

Figure 2. Logistic Regression for the Effect of Cmax after First Dose of GO on the Risk of VOD

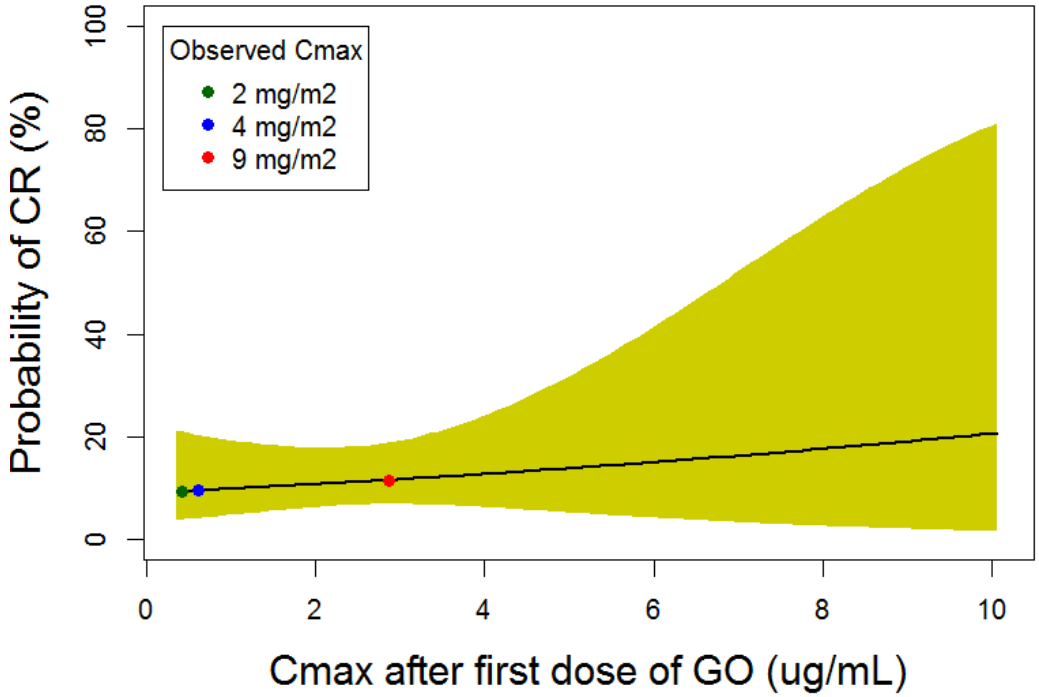


(Left: in patients with prior stem cell transplantation; right: in patients without prior stem cell transplantation. Green or purple shaded areas are 95% confidence interval for the probability of VOD. The mean values of observed Cmax following 2 mg/m^2, 4 mg/m^2 and 9 mg/m^2 were overlaid on top of the regression line for visual projection of risk but it should be noted that the exposure range was based on the estimated individual exposure levels from 9 mg/m^2 dose only, Reviewer's analysis)

The exposure-efficacy relationship for complete remission, however, was relatively flat for any exposure measures including Cmax after first dose, AUC after first dose, and average AUC (**Error! Reference source not found.**, shown for Cmax after first dose for the purpose of comparison with its effect on VOD). Covariates associated with the baseline disease condition such as baseline platelet counts, baseline bone marrow blasts, and baseline P-gp were significant predictors for

complete remission. After adjusting for these covariates, the p-value for the effect of Cmax on complete remission was 0.605. There is no clear evidence that a significant loss of efficacy is expected by reducing dose of GO from 9 mg/m^2 to 3 mg/m^2 (on Days 1, 4, 7).

Figure 3. Logistic Regression for the Effect of Cmax after First Dose of GO on Complete Remission



(*Yellow shaded area is 95% confidence interval for the probability of CR. The mean values of observed Cmax following 2 mg/m^2, 4 mg/m^2 and 9 mg/m^2 were overlaid on top of the regression line for visual projection of benefit but it should be noted that the exposure range is based on the estimated individual exposure levels from 9 mg/m^2 dose only, Reviewer's analysis)*

2.3 Summary of Labeling Recommendations

12.3 Pharmacokinetics

When gemtuzumab ozogamicin is administered at 9 mg/m^2 (2 doses, 14 days apart), the Cmax following the first dose for patients who received 9 mg/m^2 gemtuzumab ozogamicin was 3.0 mg/mL and increased to 3.6 mg/mL after the second dose.

Distribution

(b) (4) N-acetyl gamma calicheamicin dimethyl hydrazide is approximately 97% bound to human plasma proteins in vitro (b) (4)

(b) (4) Population PK analyses found (b) (4), the total volume of distribution of hP67.6 antibody (sum of V1 [6.31 L] and V2 [15.1 L]) (b) (4) to be approximately 21.4 L in patients.

Elimination

(b) (4) the clearance (CL) value of hP67.6 from plasma was 0.35 L/h after the first dose and 0.15 L/h after the second dose, a decrease of roughly 60%. The terminal plasma half-life ($t_{½}$) for hP67.6 was 62 hours after the first dose and 90 hours after the second dose.

Specific Populations

Age~~, race,~~ (b) (4)

(b) (4)

(b) (4)

(b) (4)

Drug Interaction Studies

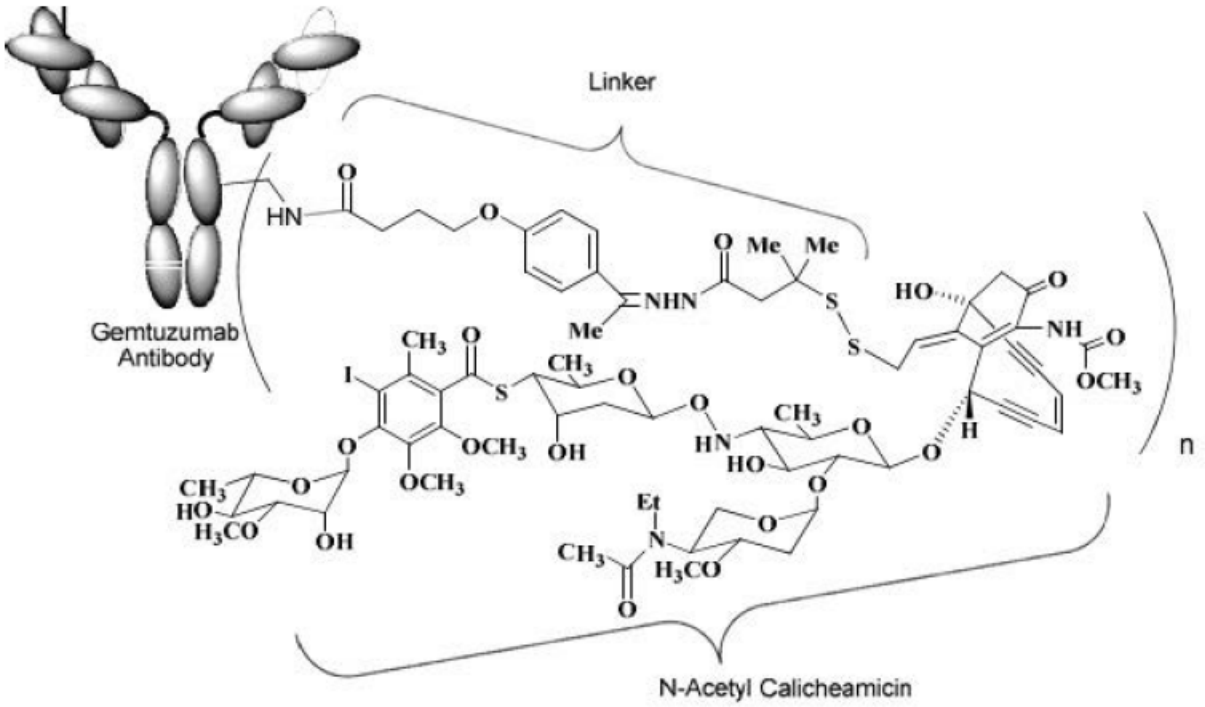
(b) (4)

3 COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Gemtuzumab ozogamicin (GO) is an antibody-drug conjugate (ADC) composed of CD33-directed monoclonal antibody (mAb; recombinant humanized immunoglobulin [Ig] G4, kappa antibody). The recombinant humanized anti-CD33 antibody is produced by mammalian cell culture using a myeloma NS0 cell line, and then covalently linked to N-acetyl-gamma calicheamicin (NAc-calicheamicin) via a bi-functional linker (**Error! Reference source not found.**). GO has approximately 50% of the antibody loaded with 4 to 6 moles calicheamicin derivative; therefore, the overall population has a loading of 2 to 3 moles calicheamicin per mole of antibody. GO has a molecular weight of 151 to 153 kDa. The antibody portion binds to CD33 antigen, a sialic acid-dependent adhesion protein found on the surface of myeloid leukemic blasts and immature normal cells of myelomonocytic lineage, but not on normal hematopoietic stem cells.

Figure 4. Gemtuzumab Ozogamicin Structure



GO has been evaluated in patients with de novo AML or refractory/relapsed AML in multiple studies including ALFA-0701 (MyloFrance 3, N=135), SWOG S0106 (N=295), MRC AML15 (N=548), NCRI AML16 (N=559), GOELAMS AML2006IR (N=126), Study 205 (N=38), Study 206 (N=71), MyloFrance 1 (N=57), and MyloFrance 2 (N=20) submitted to support the combination therapy and Study 201 (N=84), Study 202 (N=95), Study 203 (N=98), Study 101 (N=40), Study 102 (N=29), and Study 103 (N=40) submitted to support the monotherapy.

Among these studies, 3 Phase 1 studies and 5 Phase 2 studies evaluated PK of GO. Dose schedules and PK sampling in these studies are summarized in Table 1.

Table 1. Overview of GO Studies with PK Data

Protocol Number	Study Design/Objective(s)	Study Drug, Dose, Route, Duration	Number of Patients	Study Population	Study Day(s) of Dosing	Time Point(s) of Sampling (Hours)
0903A1-101-US	Phase 1, single-arm, dose escalation study to examine the safety and PK of GO	GO: 0.25, 0.5, 1, 2, 4, 5, 6, and 9 mg/m^2 as a single 2-hour IV infusion/dose (>14 days apart); maximum of 3 doses.	40	Adults with relapsed or refractory CD33-positive AML	Days 1, 15	Pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 24, 48, 72, 96 after each dose
0903A1-102-US	Pediatric Phase 1, single-arm, dose escalation study to assess safety of GO	GO: 6, 7.5, and 9 mg/m^2 as a single 2-hour IV infusion/dose for up to 2 doses. For patients aged less than 3 years, per kilogram dosing was used.	29	Children (≤17 years old) with CD33-positive refractory or relapsed AML	Days 1, 15	Pre-dose, 1, 2, 3, 4, 6, 48, 168, 216 after each dose
0903A1-103-JA	Phase 1/2, single-arm, dose escalation study to assess safety of GO	Phase 1: GO: 6, 7.5, and 9 mg/m^2 as a single 2-hour IV infusion for up to 2 doses. Phase 2: GO; 9 mg/m^2 as a single 2-hour IV infusion for up to 2 doses.	Phase 1: 20 Phase 2: 20	Japanese adults aged 18 to 70 years with relapsed or refractory CD33-positive AML in first relapse	Days 1, 15	Pre-dose, 1, 2, 3, 4, 6, 48, 168, 216 after each dose
0903B1-201-US/CA	Phase 2, single-arm, multidose study to assess safety and efficacy of GO	GO; 9 mg/m^2 as a single 2-hour IV infusion/dose for 2 or 3 doses.	84	Adults with CD33-positive AML in first relapse	Days 1, 15	Pre-dose, 1, 2, 3, 4, 6, then 2×/week for 2 weeks after each dose
0903B1-202-EU	Phase 2, single-arm, multidose, study to assess safety and efficacy of GO	GO; 9 mg/m^2 as a single 2-hour IV infusion/dose for 2 or 3 doses.	95	Adults with CD33-positive AML in first relapse	Days 1, 15	Pre-dose, 1, 2, 3, 4, 6, then 2×/week for 2 weeks after each dose
0903B1-203-US/EU	Phase 2, single-arm, multidose, study to assess safety and efficacy of GO	GO; 9 mg/m^2 as a single 2-hour IV infusion/dose for 2 or 3 doses.	98	Adults aged greater than or equal to 60 years with CD33-positive AML in first relapse	Days 1, 15	Pre-dose, 1, 2, 3, 4, 6, then 2×/week for 2 weeks after each dose
0903B1-205-	Phase 1/2, single-arm,	Phase 1: 4 dose schedules:	Phase 1: 21	Phase 1: Adults aged	Days 1, 15 (Arm	Pre-dose, 1, 2, 3, 4, 6,

Protocol Number	Study Design/Objective(s)	Study Drug, Dose, Route, Duration	Number of Patients	Study Population	Study Day(s) of Dosing	Time Point(s) of Sampling (Hours)
US/EU/AU	multicenter study to assess the safety and efficacy of GO given in combination with AraC	(1) GO 6 mg/m^2 2-hour IV, D1 and D15 (1a) GO 6 mg/m^2 D1 and 4 mg/m^2 D8, (2a) GO 6 mg/m^2 D1 and 4 mg/m^2 D8, (3a) GO 9 mg/m^2 D1, 6 mg/m^2 D8 All GO doses except 1a were combined with AraC 100 mg/m^2 D1 to 7. Phase 2: Dose schedule "2a" from Phase 1.	 Phase 2: 17	greater than or equal to 18 years with relapsed or refractory AML or patients aged greater than or equal to 60 years with de novo untreated CD33-positive AML Phase 2: Untreated adults aged greater than or equal to 60 years with de novo CD33-positive AML	1); Days 1, 8 (Arms 1a, 2a, and 3a)	48, 96, 168, 170, 174, 216, 264, 336, 504 post-first GO dose
0903B1-206-US/EU/AU	Phase 1/2, single-arm, multicenter study to assess safety and efficacy of GO given in combination with AraC and DNR	Phase 1: 3 dose schedules: a) AraC 100 mg/m^2 IV, D1-7; DNR 45 mg/m^2 IV, D1-3; GO 6 mg/m^2 D4. b) AraC 100 mg/m^2 D1-7; DNR 45 mg/m^2 D1-3; GO 9 mg/m^2 D4. c) AraC 200 mg/m^2 D1-7; DNR 45 mg/m^2 D1-3; GO 9 mg/m^2 D4. Phase 2: Dose schedule "a" from Phase 1	Phase 1: 22 Phase 2: 49	Phase 1: Adults aged greater than or equal to 18 years and less than 60 years with de novo CD33-positive AML or adults greater than or equal to 18 years with CD33-positive relapsed or refractory AML	Day 4	Pre-dose, 2, 24, 48, 72, 192, 264 post GO dose

(Source: Summary of Clinical Pharmacology, Table 3, page 15)

GO was granted an accelerated approval on May 17, 2000 as a monotherapy with dose of 9 mg/m^2 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 cytotoxic chemotherapy. During the post-marketing period, rates of fatal hepatotoxicity and veno-occlusive disease (VOD) were found to be higher than those observed during the registration trial. Thus, boxed warnings highlighting risk of VOD in patients who received 9 mg/m^2 of GO were added in the labeling. To fulfill a PMR to confirm the clinical benefit of GO, the SWOG study was conducted to compare the efficacy of GO + daunorubicin (DNR)/cytarabine (AraC) with DNR/AraC. The GO dose of 6 mg/m^2 was used in the randomized trial in de novo patients ≤60 years of age. The study did not show better efficacy with GO but showed higher induction toxicity with GO. FDA concluded there was no clinical benefit of GO and the sponsor (Wyeth) withdrew Mylotarg® from the market in November 2011.

The Applicant conducted an additional randomized trial (ALFA-701) with a fractionated lower doses of 3 mg/m^2 in combination with DNR/AraC in de novo AML patients (N=271) between 50 to 70 years of age. The results from ALFA-701 showed clinical benefit of GO with no significant difference in 30-day mortality between GO+DNR/AraC arm and DNR/AraC arm. The Applicant submitted this study under a new BLA for 2 indications with different dosing schedules including the originally approved and withdrawn dose of 9 mg/m^2 as a monotherapy.

The primary efficacy endpoint for ALFA-701 was EFS, not overall survival (OS). Since the surrogacy of EFS for OS has not been established, the Applicant performed meta-analyses as well as analysis with individual patient data. The individual patient data were from 5 clinical trials and the data for meta-analyses were from 33 published studies for de novo AML. The EFS was defined as time from randomization to induction failure, relapse or death due to any cause. Induction failure was defined as failure to achieve a CR (including CR, or CR with incomplete blood count recovery) within 60 days of randomization. However, the definition of the EFS in the individual patient data meta-analysis was different from the one used in trial ALFA-701, in which the determination of induction failure was not limited to the first 60 days from randomization and the date of induction failure was the date of post-induction assessment. Nonetheless, the Applicant's meta-analyses estimated the correlation between EFS and OS and they were poorly correlated (R^2 was estimated to be ~0.5 by various methods, see statistical reviewer's review for details).

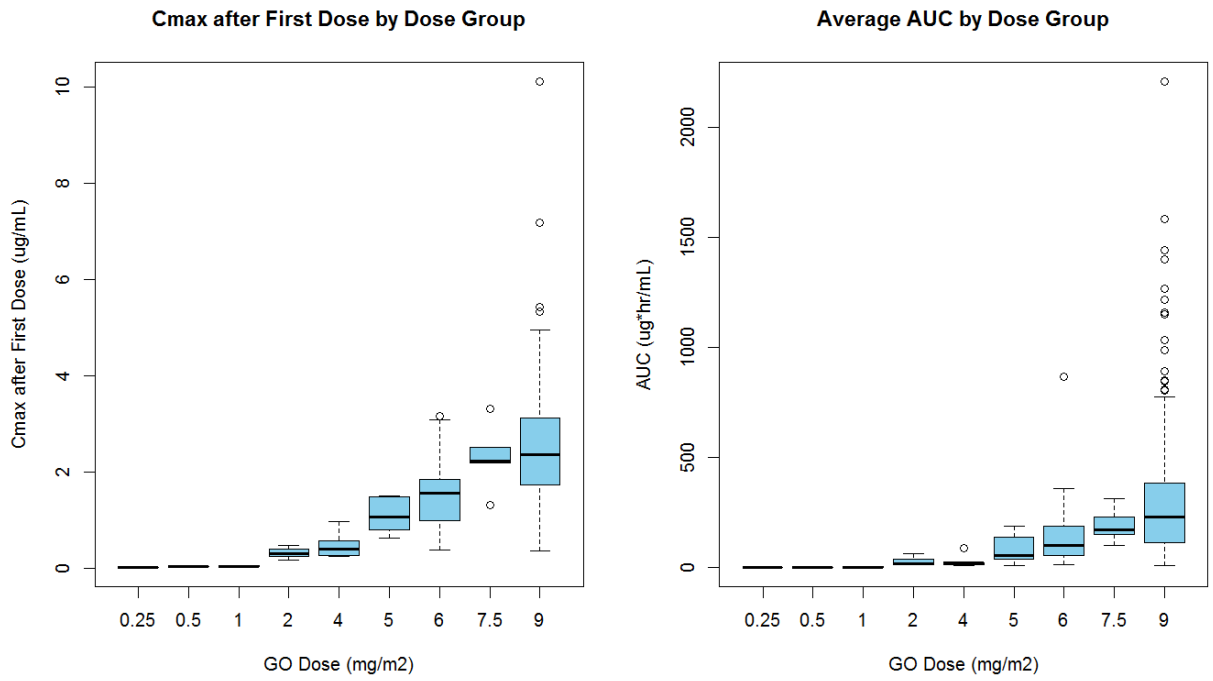
3.2 General Pharmacological and Pharmacokinetic Characteristics

3.3 Clinical Pharmacology Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The pivotal trials for combination therapy with DNR and AraC (ALFA-0701) did not collect any PK measurements. Thus, the supportive evidence of effectiveness of GO in combination with DNR/AraC was inferred by observed PK/PD data with GO as a single agent. The exposure of hP67.6 appears to increase more than proportionally as GO dose increases (**Error! Reference source not found.**). Cmax after first dose and AUC following 3 mg/m^2 were significant lower than those with 9 mg/m^2.

Figure 5. Exposure of Antibody of GO (hP67.6) Following a Single Dose of GO at Doses Ranging from 0.25 mg/m^2 to 9 mg/m^2



(Reviewer's analysis)

However, the pharmacodynamics data for the target antigen saturation indicate that CD33 site is saturated with GO dose of 2 mg/m^2 or above (Figure 1). Therefore, the fractionated dose of 3 mg/m^2 given in combination with DNR/AraC is likely to be effective in patients with AML.

3.3.2 Is the proposed general dosing regimen appropriate for the general patient population for which the indication is being sought?

The proposed dosing regimen (fractionated dosing of 3 mg/m^2 on Days 1, 4, 7) in combination with DNR and AraC for patients with de novo AML appears to be adequate. (b) (4)

Exploratory analyses for exposure-response for efficacy and safety indicate that a fractionated lower dose has the potential to reduce the risk for VOD but preserve the efficacy of GO. Furthermore, literature data reported considerable efficacy of GO with a fractionated dose of 3 mg/m^2 although dosing schedule is slightly different. In AML-17 study, two different dosing schedules of GO (A: 3 mg/m^2 on Days 1, 3, 5; B: 6 mg/m^2 on Day 1, 3 mg/m^2 on

Day 8) were compared with the best supportive care in older patients with newly diagnosed AML[1]. The complete remission rate was 21% (A) and 18% (B). No VOD was observed in both dose groups. Another study with a fractionated dose of 3 mg/m^2 on Days 1, 4, and 7 showed complete remission rate of 26% in patients with relapsed AML and no VOD[2]. Therefore, a study to evaluate the efficacy and safety of a fractionated dose of 3 mg/m^2 is recommended.

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

No. The population PK analysis for the effect of age, sex, or renal/hepatic impairment did not indicate any need for dose adjustment of GO.

3.3.4 What is the incidence (rate) of the formation of the anti-drug antibodies (ADA)? Do the ADAs have neutralizing activity?

GO ADC was not measured in any of the clinical studies in patients with AML and the assay for a GO neutralizing antibody was not developed.

3.4 Clinical PK and/or PD assessments

3.5 Applicant's Analysis

3.5.1 Population PK Analyses

The Applicant conducted population PK analyses to describe the PK of total hP67.6 and unconjugated calicheamicin in adults with AML based on pooled data (N=407, Table 2). The dataset for pooled analysis of hP67.6 comprised 5643 concentrations obtained from 407 patients, including 505 (9%) concentrations <LLOQ. The dataset for the pooled analysis of unconjugated calicheamicin comprised 4281 concentrations obtained from 338 patients, including 730 (17%) concentrations <LLOQ.

The effects of covariates affecting the PK of hP67.6 and/or unconjugated calicheamicin were investigated and those covariates included in the analyses are summarized in Table 3 and Table 4. Drug-drug interactions between GO and AraC/DNR were also evaluated. Since PK measurements from the pivotal trial for the combination therapy (ALFA-701) were not obtained at all, simulated concentrations for subjects enrolled in ALFA-701 using the population PK model were obtained to

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[1] Amadori S, Suciu S, et al., Sequential combination of gemtuzumab ozogamicin and standard chemotherapy in older patients with newly diagnosed acute myeloid leukemia: results of a randomized Phase III trial by the EORTC and GIMEMA Consortium (AML-17). J Clin Oncol, 2013. 31:4424-4430

[2] Taksin, A.L., et al., High efficacy and safety profile of fractionated doses of Mylotarg as induction therapy in patients with relapsed acute myeloblastic leukemia: a prospective study of the alfa group. Leukemia, 2007. 21(1): p. 66-71.

be utilized for further PKPD assessment.

The PK of GO was described using a 2-compartment model with linear and time-dependent clearance.

$$CL = CL_1 + CL_t$$

$$CL_t = CL_2 \bullet e^{(-k_{dec} \bullet Time)}$$

where total clearance (CL) is a sum of time-dependent clearance (CL_t) and linear clearance (CL_l), and k_{deg} is the decay coefficient of the time-dependent clearance.

The PK of unconjugated calicheamicin was described with a 2-compartment with linear clearance and an input rate of formation obtained by calculating the fraction of calicheamicin that appears in the circulation over time using the total hP67.6 eliminated and converted to unconjugated calicheamicin through stoichiometry.

$$\frac{K_f}{F} \times HP67$$

$$HP67 = PCL_{ij} \times HP_{ij} \times 0.0228$$

where K_f/F is the apparent faction of calicheamicin that appears in circulation over time, HP67 is the potential rate of formation of unconjugated calicheamicin into the central compartment if all eliminated antibody is free of calicheamicin, PCL_{ij} is the total antibody clearance of the $_i$th patient at time t_j taken from the post-hoc empirical Bayes estimates (EBEs) of the final total antibody model, HP is the total antibody concentration observed in the $_i$th patient at time t_j in mg/L, and 0.0228 is the stoichiometric conversion from total antibody to unconjugated calicheamicin assuming 2.5 conjugated drug molecules per antibody and a molecular weight of 150,000 grams/mol and 1368 grams/mol for total hP67.6 antibody and calicheamicin, respectively.

3.5.1.1 Analysis Dataset

The analysis datasets utilized in the population PK analysis are summarized in Table 2

Table 2. Summary of Data included in the Population PK Analysis

Study	Design	Drug, Dose	Number of Subjects	Population
101	Phase 1, single-arm, dose-escalation	GO 0.25, 0.5, 1, 2, 4, 5, 6, 9 mg/m^2 (max no. of doses:3)	40	Adults with relapsed or refractory CD33-positive AML
103	Phase 1/2, single-arm	Phase 1: GO 6, 7.5, 9 mg/m^2 Phase 2: 9 mg/m^2	Phase 1: 20 Phase 2: 20	Japanese adults with relapsed or refractory CD33-positive AML in first relapse
201	Phase 2, single-arm	GO 9 mg/m^2	84	Adults with CD33-positive AML in first relapse
202	Phase 2, single-arm	GO 9 mg/m^2	95	Adults with CD33-positive AML with first relapse

203	Phase 2, single-arm	GO 9 mg/m^2	98	Adults >=60 years with CD33-positive AML in first relapse
205	Phase 1/2, single-arm	Phase 1: GO 6 mg/m^2 + AraC 100 mg/m^2 (D1-7) (1a) GO 6 mg/m2 D1 + 4 mg/m^2 D8 (1b) GO 6 mg/m2 D1 + 4 mg/m^2 D8 + AraC 100 mg/m^2 D1-7 (1c) GO 9 mg/m^2 D1 + 6 mg/m^2 D8 + AraC 100 mg/m^2 D1-7 (1d) GO 9 mg/m^2 D1 + 7 mg/m^2 D8 + AraC 200 mg/m^2 D1-7 Phase 2: Dose schedule(1b) from Dose schedule from Phase 1	Phase 1: 21 Phase 2: 17	Phase 1: adults >= 18 years and <60 years with relapsed or refractory AML or patients >=60 years with de novo CD33-positivie AML Phase 2: Untreated adults >=60 years with de novo CD33-positive AML
206	Phase 1/2, single-arm	Phase 1: (1) AraC 100 mg/m^2, D1-7 + DNR 45 mg/m^2, D1-3 + GO 6 mg/m^2 D4 (2) AraC 100 mg/m^2 D1-7 + DNR 45 mg/m^2 D1-3 + GO 9 mg/m^2 D4 (3) AraC 200 mg/m^2 D1-7 + DNR 45 mg/m^2 D1-3 + GO 9 mg/m^2 D4 Phase 2: Dose schedule (1) from Phase 1	Phase 1: 22 Phase 2: 49	Phase 1: adults >= 18 years and <60 years with de novo AML or adults >= with relapsed or refractory CD33-positive AML Phase 2: adults >=18 and <60 years with de novo CD33-positive AML

Table 3. Summary of Baseline Categorical Covariates by Study

Covariate	Category	0903A1-101-US N=39	0903A1-103-JA N=20	0903B1-201-US/CA N=81	0903B1-202-EU N=93	0903B1-203-US/EU N=91	0903B1-205-AU/EU/US N=19	0903B1-206-AU/EU/US N=64	TOTAL N=407
Sex	Male	20 (51%)	11 (55%)	42 (52%)	52 (56%)	52 (57%)	9 (47%)	41 (64%)	227 (56%)
	Female	19 (49%)	9 (45%)	39 (48%)	41 (44%)	39 (43%)	10 (53%)	23 (36%)	180 (44%)
Race	White	32 (82%)	0 (0%)	73 (90%)	92 (99%)	88 (97%)	18 (95%)	59 (92%)	362 (89%)
	Black	1 (3%)	0 (0%)	2 (2%)	1 (1%)	2 (2%)	0 (0%)	2 (3%)	8 (2%)
	Asian	4 (10%)	20 (100%)	2 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	26 (6%)
	Other	2 (5%)	0 (0%)	4 (5%)	0 (0%)	1 (1%)	1 (5%)	3 (5%)	11 (3%)
Baseline ECOG Performance Score	0	15 (38%)	0 (0%)	48 (59%)	48 (52%)	27 (30%)	7 (37%)	25 (39%)	152 (37%)
	1	24 (62%)	12 (60%)	25 (31%)	37 (40%)	43 (47%)	8 (42%)	34 (53%)	191 (47%)
	2	0 (0%)	7 (35%)	5 (6%)	6 (6%)	17 (19%)	4 (21%)	5 (8%)	51 (13%)
	3	0 (0%)	1 (5%)	0 (0%)	1 (1%)	2 (2%)	0 (0%)	0 (0%)	7 (2%)
	4	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
	Unknown	0 (0%)	0 (0%)	3 (4%)	0 (0%)	2 (2%)	0 (0%)	0 (0%)	5 (1%)
Prior Hydroxyurea	Yes	7 (18%)	0 (0%)	17 (21%)	15 (16%)	38 (42%)	19 (100%)	13 (20%)	109 (27%)
	No	32 (82%)	20 (100%)	64 (79%)	78 (84%)	53 (58%)	0 (0%)	51 (80%)	298 (73%)
Concomitant Hydroxyurea	Yes	2 (5%)	0 (0%)	1 (1%)	1 (1%)	0 (0%)	19 (100%)	11 (17%)	34 (8%)
	No	37 (95%)	20 (100%)	80 (99%)	92 (99%)	91 (100%)	0 (0%)	53 (83%)	373 (92%)
de novo	Yes	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	13 (68%)	51 (80%)	64 (16%)
	No	39 (100%)	20 (100%)	81 (100%)	93 (100%)	91 (100%)	6 (32%)	13 (20%)	343 (84%)
Combination Treatment	None	39 (100%)	20 (100%)	81 (100%)	93 (100%)	91 (100%)	0 (0%)	0 (0%)	324 (80%)
	1	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	19 (100%)	0 (0%)	19 (5%)
	2	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	64 (100%)	64 (16%)
CD33 Status	Positive	38 (97%)	20 (100%)	81 (100%)	93 (100%)	90 (99%)	15 (79%)	57 (89%)	394 (97%)
	Negative	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (5%)	1(2%)	3 (1%)
	Missing	1 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (16%)	6 (9%)	10 (2%)

Source: ePharmacology Artifact ID Numbers 11327927, 11327929, 11327903, 11327931.
AU=Australia; CA=Canada; CD33=CD33 immunophenotype; ECOG=Eastern Cooperative Oncology Group; EU=Europe; hP67.6=total antibody; ID=identification; JA=Japan; N=number of patients; US=United States.

Table 4. Summary of Baseline Categorical Covariates by Dose Level

Covariate	Category	Dose Level ≤3 mg/m^2 N=13	Dose Level >3 mg/m^2 and ≤6 mg/m^2 N=91	Dose Level >6 mg/m^2 N=303
Sex	Male	5 (38%)	55 (60%)	167 (55%)
	Female	8 (62%)	36 (40%)	136 (45%)
Race	White	11 (85%)	76 (84%)	275 (91%)
	Black	0 (0%)	3 (3%)	5 (2%)
	Asian	2 (15%)	7 (8%)	17 (6%)
	Other	0 (0%)	5 (5%)	6 (2%)
Baseline ECOG Performance Score	0	6 (46%)	32 (35%)	132 (44%)
	1	7 (54%)	49 (54%)	127 (42%)
	2	0 (0%)	9 (10%)	35 (12%)
	3	0 (0%)	1 (1%)	3 (1%)
	4	0 (0%)	0 (0%)	1 (0%)
	Unknown	0 (0%)	0 (0%)	5 (2%)
Prior Hydroxyurea	Yes	0 (0%)	30 (33%)	79 (26%)
	No	13 (100%)	61 (67%)	224 (74%)
Concomitant Hydroxyurea	Yes	1 (8%)	24 (26%)	9 (3%)
	No	12 (92%)	67 (74%)	294 (97%)
de novo	Yes	0 (0%)	58 (64%)	6 (2%)
	No	13 (100%)	33 (36%)	297 (98%)
Combination Treatment	None	13 (100%)	25 (27%)	286 (94%)
	1	0 (0%)	15 (16%)	4 (1%)
	2	0 (0%)	51 (56%)	13 (4%)
CD33 Status	Positive	12 (92%)	81 (89%)	301 (99%)
	Negative	0 (0%)	2 (2%)	1 (0%)
	Missing	1 (8%)	8 (9%)	1 (0%)

Source: ePharmacology Artifact ID Numbers 11327928, 11327930.
CD33=CD33 immunophenotype; ECOG=Eastern Cooperative Oncology Group; hP67.6=total antibody; JA=Japan; ID=identification; N=number of patients.

3.5.1.2 Results

The PK of GO was described using a 2-comparment model with linear clearance and time-dependent clearance, with fixed effects of baseline body weight and total dose on CL_1 and V_1 and fixed effects of dose to account for the wide range of dose levels in the analysis population. The PK of unconjugated calicheamicin was described using a 2-compartment model with linear clearance and a rate of formation based on the total antibody elimination rate, with the fixed effect of baseline body weight on CL/F and V1/F.

The equations below describe the final model estimation of typical values of CL_1, V_1, CL_2, and k_{des} before adding inter-individual variability:

$$CL_1 = 0.103 \text{ L/h} \bullet (BWT/77)^{0.75} \bullet (DOSE/15.75)^{-0.912} \bullet (1-0.256 \bullet [BALB-3.70 \text{ g/dL}])$$

$$V_1 = 6.31 \text{ L} \bullet (BWT/77)^{1} \bullet (DOSE/15.75)^{-0.443} \bullet (1-0.162 \bullet SEX_F) \bullet (BALB/3.70 \text{ g/dL})^{-0.433}$$

$$CL_2 = 2.98 \text{ L/h}$$

$$k_{des} = 0.867 \text{ h}^{-1} \bullet (1-0.0153 \bullet [BMAR-73.0\%]) \bullet (BBC/14.5)^{-0.0567} \bullet (1-0.434 \bullet COMB_2) \bullet (1-0.886 \bullet COMB_1)$$

The final model estimated parameters are summarized in Table 5.

Table 5. PK Parameters for Total Antibody Estimated from Final Model

Parameter	Final Model for hP67.6 Analysis						
	Fit Result OFV=-1866.901				Nonparametric Bootstrap Result OFV=-1891.61		
	Estimate	95% CI[a]		Shrinkage	Estimate[b]	95% CI[c]	
		Lower	Upper	%	(Median)	Lower	Upper
CL_1 (L/h)	0.103	0.0910	0.115	--	0.100	0.0874	0.114
DOSE on CL_1	-0.912	-1.12	-0.706	--	-0.897	-1.23	-0.493
BALB on CL_1	-0.256	-0.409	-0.103	--	-0.245	-0.434	-0.0683
V_1 (L)	6.31	5.87	6.75	--	6.37	5.90	6.83
DOSE on V_1	-0.443	-0.581	-0.305	--	-0.497	-0.684	-0.316
BALB on V_1	-0.433	-0.784	-0.0820	--	-0.421	-0.791	-0.0697
SEX_F *on* V_1	-0.162	-0.246	-0.0780	--	-0.171	-0.250	-0.0838
Q (L/h)	0.0924	0.0720	0.113	--	0.0895	0.0701	0.112
V_2 (L)	15.1	11.7	18.6	--	15.7	11.1	21.5
CL_2 (L/h)	2.98	1.87	4.09	--	2.97	1.82	4.76
k_{des} (h^{-1})	0.867	0.555	1.18	--	0.822	0.537	1.19
BMAR (%) on k_{des}	-0.0.0153	-0.0230	-0.00800	--	-0.0142	-0.0212	-0.00644
BBC (%)on k_{des}	-0.0567	-0.09400	-0.0200	--	-0.0590	-0.103	-0.0181
$COMB_2$ *on* k_{des}	-0.434	-0.830	-0.0380	--	-0.462	-0.703	-0.0889
$COMB_1$ *on* k_{des}	-0.886	-0.962	-0.810	--	-0.858	-0.968	-0.669
CL_1 ω^2 (%CV)	0.680 (82.5)	0.353	1.01	15.6	0.666	0.543	0.800
V_1 ω^2 (%CV)	0.180 (42.4)	0.0380	0.322	15.3	0.176	0.132	0.246
Q ω^2 (%CV)	2.51 (158)	1.98	3.04	24.7	2.35	1.50	3.28
V_2 ω^2 (%CV)	1.13 (106)	0.560	1.70	49.5	1.21	0.771	1.60
CL_2 ω^2 (%CV)	2.98 (173)	0.942	5.02	32.7	2.73	1.78	3.99
k_{des} ω^2 (%CV)	1.64 (128)	0.944	2.34	36.8	1.43	1.01	2.02
Res Prop Err	0.329	0.307	0.351	7.82	0.330	0.310	0.352

(Source: pmar-eqdd-b176a-snda493, Table 16, page 78)

The equation below describes the final model estimation of typical values of CL/F, V_1/F and K_f/F for unconjugated calicheamicin before inter-individual variability.

$CL/F = 1.21\ L/h \bullet (BWT/77)^{0.75}$

$V_1/F = 96.9\ L \bullet (BWT/77)^{1}$

$K_f/F = 0.013$

where BWT is the baseline body weight.

The generation of unconjugated calicheamicin reaching the central compartment from total antibody eliminated over time is:

$0.013 \bullet PCL \bullet HP \bullet 0.0228$

where PCL is the patient total antibody clearance, HP is the total hP67.6 antibody concentration, 0.0228 is the stoichiometric conversion factor between total antibody and unconjugated calicheamicin, and 0.013 is the apparent proportion of total hP67.6 antibody eliminated, which releases calicheamicin in the systemic circulation (K_f/F). The final estimated PK parameters for unconjugated calicheamicin are summarized in Table 6.

Table 6. PK Parameters for Unconjugated Calicheamicin Estimated from Final Model

Parameter	Final Model for Unconjugated Calicheamicin (M3 Include Data < LLOQ)[a]						
	Fit Result OFV=381.088				Nonparametric Bootstrap Result OFV=373.226		
	Estimate	95% CI[b]		Shrinkage	Estimate[c]	95% CI[d]	
		Lower	Upper	%	(Median)	Lower	Upper
CL/F (L/h)	1.21	0.857	1.56	--	1.30	0.973	1.63
V_1/F (L)	96.9	89.9	104	--	96.7	90.1	103
Q/F (L/h)	2.93	2.30	3.56	--	2.92	2.40	3.57
V_2/F (L)	665	326	1004	--	610	430	872
K_f/F	0.013	0	0.030	--	0.0136	0.00122	0.0556
$CL_1/F\ \omega^2$ (%CV)	0.681 (82.5%)	0.170	1.19	32.7	0.566	0.318	1.10
$V_1/F\ \omega^2$ (%CV)	0.244 (49.4%)	0.160	0.330	17.8	0.243	0.183	0.324
$Q/F\ \omega^2$ (%CV)	1.32 (115%)	0.53	2.11	34.8	1.34	0.918	1.90
$V_2/F\ \omega^2$ (%CV)	0.732 (85.6%)	0.21	1.25	52.5	0.671	0.197	1.29
$K_f/F\ \omega^2$ (%CV)	7.93 (282%)	2.83	13.03	52.9	8.21	3.69	16.3
Res Prop Err	0.467	0.432	0.502	11.1	0.466	0.431	0.502
$CL/F - V_1/F\ \omega^2$ (%CV)	0.249 (49.9%)	0.0600	0.442	--	0.217	0.0922	0.346

(Source: pmar-eqdd-b176a-snda493, Table 20, page 100)

The Applicant imputed missing data for body weight, height, baseline height, body surface area (BSA), baseline BSA, baseline serum creatinine, baseline creatinine clearance, baseline total bilirubin, baseline alanine aminotransferase (ALT), baseline aspartate aminotransferase (AST), baseline albumin, baseline peripheral blast count, baseline percentage blast in bone marrow, and CD33 immuno-phenotype status. Among them, values used for labeling statement were summarized.

Baseline creatinine clearance was missing form STID (b) (6) and the values were derived from AGE, body weight and baseline serum creatinine. However, body weight for STID (b) (6) was also missing so the value was imputed as the population median baseline value, baseline serum creatinine values for STID (b) (6) were missing and the values were imputed from the most recent post-baseline value within the first 4 days after the first dose. Since some of these patients were utilized in evaluation of the effect of hepatic impairment, the Applicant's conclusion on the effect of hepatic impairment is invalid (See section 3.5.1.4)

Baseline total bilirubin was missing for STID (b) (6) and the value was population from the most recent post-baseline value within the first 4 days after the first dose. Baseline alanine aminotransferase was missing for 23 patients. The value was population form the most recent post-baseline value within the first 4 days after the first dose for STID (b) (6), (b) (6). Baseline aspartate aminotransferase was missing for 6 patients. The value was population from the most recent post-baseline value within the first 4 days after the first dose for STID (b) (6).

3.5.1.3 R*enal Impairment*

The baseline creatinine clearance was not identified as a statistically significant covariate on the PK of GO. The post-hoc estimated clearance in normal (N=209), mild (N=149), moderate (N=47) and severe (N=1) were similar. The renal impairment does not appear to affect the PK of GO.

3.5.1.4 Hepatic Impairment

Baseline albumin was a significant covariate on CL_1 and V_1, and combination therapy was also a significant covariate on k_{deg}. The effect of hepatic impairment was assessed using NCI ODWG criteria. The Applicant identified 6 patients with moderate hepatic impairment ((b) (6), (b) (6)). Among them, AST value for (b) (6) was imputed due to missing data and 2 patients (b) (6) received GO as a combination therapy with AraC or AraC+DNR. Considering confounders of combination therapy and dose, the number of subjects categorized into moderate hepatic impairment on the PK of GO was too few to make a conclusion.

3.5.1.5 Drug Interactions

The Applicant claims no effects of concomitant use of DNR, AraC, and hydroxyurea on the PK of GO. However, co-administration of AraC only or AraC along with DNR on the GO PK was identified as a significant predictor of k_{deg} in the population PK analyses. The rate of decrease in clearance of GO gets slower when AraC or AraC/DNR is co-administered. Also none of patients enrolled in ALFA-701 received hydroxyurea concomitantly.

Furthermore, the Applicant evaluated the effect of GO on PK of AraC using data from Study 206 only. Among the data from Study 206, 132 measurements for AraC concentration obtained from 49 patients were below LLOQ. Due to sparsity of the samples, the evaluation using population PK was not performed. Instead, the pre-dose and post-dose concentrations were summarized and ANOVA were reported (Table 7). Based on this approach, the Applicant claimed that there was no statistically significant difference (137 vs. 114 ng/mL, p=0.513) between concentrations of cytarabine following 100 mg dose of AraC alone and those following 100 mg dose of AraC along with GO, and thus concluded GO did not affect the PK of AraC. However, the exposure in 3 subjects following 200 mg dose of AraC which is the recommended dose of AraC in combination therapy, showed a huge difference (1797 vs. 65.1 ng/mL). Thus, we cannot clearly rule out the drug interaction of GO with AraC.

Table 7. Summary of Cytarabine Concentration by Nominal Time Post-Dose of AraC

AraC Dose Level (mg/m^2)	Predose				AraC Alone				AraC With GO			
	NTPD 0 hours (ng/mL)				NTPD 48 hours (ng/mL)				NTPD 96 hours (ng/mL)			
	N	GM	95% CI		N	GM	95% CI		N	GM	95% CI	
			Lower	Upper			Lower	Upper			Lower	Upper
100	33	35.4	30.8	40.8	36	137	87.9	214	37	114	77.7	168
200	3	38.8	17.6	85.6	3	1797	118	27361	3	65.1	24.4	173

Source: ePharmacology Artifact ID Number 11335563.
AraC=cytarabine; CI=confidence interval; GM=geometric mean; ID=identification; LLOQ=lower limit of quantitation; N=number of patients; NTPD=nominal time postdose.
Patients with data < LLOQ were not included in this table; there were 8, 5, and 3 patients with data < LLOQ predose, 48, and 96 hours postdose of 100 mg/m^2 of AraC, respectively. There was 1 patient with predose 200 mg/m^2 of AraC < LLOQ.

(Source: pmar-eqdd-b176a-snda493, Table 29, page 110)

The Applicant evaluated the effect of GO on daunorubicin (DNR) using literature data. The Applicant claims the PK of DNR following co-administration with AraC and GO did not show difference between reported parameters with DNR 50 mg/m^2 dose only and its estimated parameters following DNR 45 mg/m^2 along with AraC and GO in Study 206. However, the majority of daunorubicin concentrations in Study 206 were below LLOQ (95%) while the literature reported its PK parameters adequately. Given that PK parameter estimates were not feasible for daunorubicin, the Applicant reported the comparison of the PK of its metabolite, daunorubicinol, instead. Based on the comparison of daunorubicinol PK, the Applicant claims there is no "gross difference"

between DNR alone and DNR with AraC and GO. As shown in Table 8, however, the clearance and volume of distribution for the metabolite following DNR along with GO (N=69) were 76.0 L/hr and 292 L while those following DNR alone (N=16) were 54.3 L/hr and 190 L, respectively. Also it should be noted that the DNR dose used in Study 206 was 45 mg and the recommended dose of DNR for the combination therapy is 60 mg. Nevertheless, drug interactions between GO and DNR/AraC would not raise any issues for dose adjustment strategy since the efficacy and safety with the combination therapy have been established.

Table 8. Comparison of Daunorubicinol PK between Study 206 and Reported in Literature

Parameter	Study 0903B1-206-US/EU/AU N=69		Callies et al19 N=16	
	Estimate (%SE)	IIV (%)	Estimate (%SE)	IIV (%)
CLm/fm (L/h)	76.0 (4.05)	23.9	54.3 (7.46)	27.3
Vm/fm (L)	292 (214)	31.6	190 (27.5)	74.9
Vp/fm (L)	1360(187)	5.93	737 (14.5)	42.5
Qm/fm (L/h)	3640 (1420)	27.5	2050 (17.4)	NA
Res Prop Error	35.2% (3.4)	NA	21.6% (13.2)	NA

Source: ePharmacology Artifact ID Number 11339257.
AU=Australia; CLm/fm=apparent clearance of metabolite; EU=European Union; fm=fraction of daunorubicin dose converted into daunorubicinol; ID=identification; IIV=interindividual variability; m=metabolite; N=total number of subjects; NA=not applicable; Qm/fm=apparent intercompartmental clearance; Res Prop Err=residual proportional error; SE=standard error; US=United States; Vm/fm=apparent volume of distribution of the central compartment; Vp/fm=apparent volume of distribution of peripheral compartment.

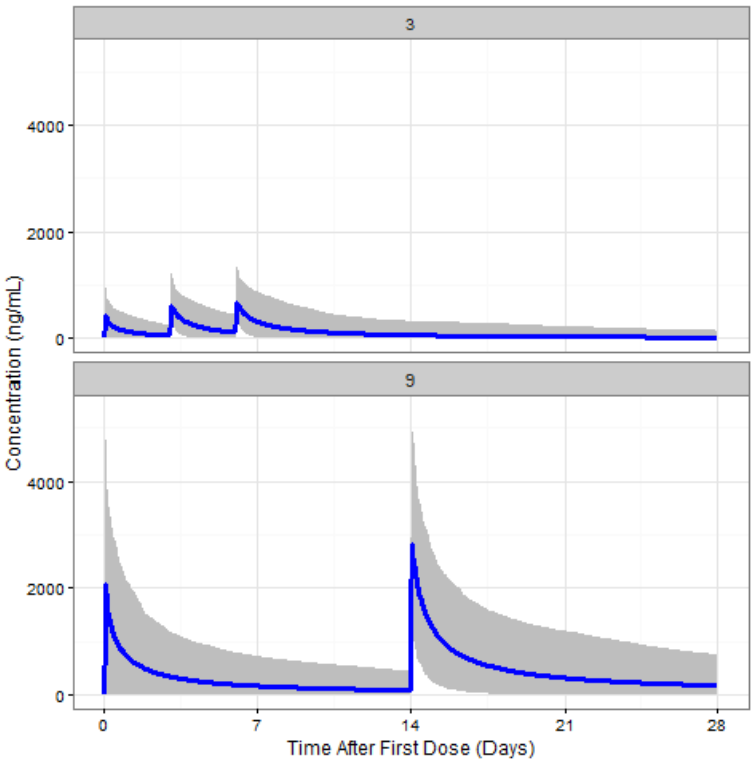
(Source: pmar-eqdd-b176a-snda493, Table 31, page 112)

3.5.2 Simulations

Since PK was not collected in Study ALFA-701, simulations were performed with the final population PK model to predict the exposure of total antibody and unconjugated calicheamicin using the actual dose and the baseline covariates data for patients who were enrolled in ALFA-0701 and received GO. It was assumed every patient received 3 doses of 3 mg/m^2 of GO, on Days 1, 4, and 7 for induction therapy. However, the simulation could not adequately predict the exposures in patients in ALFA-0701 since the observed data with the fractionated dose of GO in combination with DNR/AraC in other studies were obtained only from 13 patients and these are too few to be utilized for predicted exposures in 270 patients. Moreover, the inter-individual variabilities for PK parameters were too large to adequately predict exposures in individuals using baseline covariates data.

Other simulations were performed to predict and compare total hP67.6 antibody and unconjugated calicheamicin concentration-time course following GO 9 mg/m^2 on Days 1 and 15 and following an alternative, fractionated dosing regimen of 3 mg/m^2 on Days 1, 4, and 7 (hP67.7 in **Error! Reference source not found.**). The results showed plasma hP67.6 antibody exposures increases over time with repeated dosing, mainly due to the significant decline in total CL after the initial dose, as CL_t approaches zero with time, which is also consistent with the PK of antibodies that target B-cell receptors presenting target-mediated drug disposition.

Figure 6. Simulation of Total Antibody Concentration Over Time Following GO 3 mg/m^2 on Days 1, 4, and 7 in combination with AraC/DNR (upper) or GO 9 mg/m^2 on Days 1 and 15 as Monotherapy (lower) for Typical Patients



(Source: pmar-eqdd-b176a-snda493, Figure 40, page 102)

3.5.3 Exposure-Response Analyses

The Applicant's exposure-response analysis for efficacy was performed for proportion of patients who achieved complete remission or complete remission without full recovery of platelet. Since complete remission without full recovery of platelet cannot be considered as an adequate efficacy endpoint, all of the analysis results were not acceptable.

3.6 Reviewer's Analyses

3.6.1 Introduction

The Applicant's ER for efficacy used combined endpoint of complete remission and complete remission without full recovery of platelet as the efficacy endpoint. Thus, the reviewer performed an ER analysis for complete remission with full platelet recovery only. Moreover, ER analyses for safety endpoints were also performed to evaluate the potential benefits of alternative dosing regimen

for monotherapy. Based on the efficacy and safety ER analysis results, fractionated dosing regimen with a lower dose, e.g., 3 mg/m^2, could improve the risk/benefit profile for monotherapy. Thus, the potential benefit of the fractionated dosing regimen(s) was also evaluated.

3.6.2 Objectives

- To evaluate the exposure-response relationships for complete remission
- To evaluate the exposure-response relationships for safety endpoints, including VOD and liver toxicities
- To evaluate the clinical benefit with fractionated dose for monotherapy

3.6.3 Datasets

Datasets utilized for the analyses are summarized below.

Table 9. Analysis Data Sets

Study Number	Name	Link to EDR
Omar-eqdd-b176a-snda-491	Comb.xpt	\\CDSESUB1\evsprod\BLA761060\0001\m5\datasets\pmar-eqdd-b176a-snda-491\analysis\legacy\datasets
Study 201, 202, 203	Demog+MaxResponseIWG pivotal CR.csv	N/A

3.6.4 Exposure-Response Analysis Results

3.6.4.1 Exposure-Safety Analyses

Exposure-response analyses for safety endpoints related to liver toxicity including AST, ALT, total bilirubin did not show significant effect of any exposure measures on these endpoints. However, the effect of exposure on VOD was significant with any exposure measures and Cmax after first dose showed the most significant effect on VOD. Based on covariate analyses using baseline risk factors, prior stem cell transplantation was a significant predictor for the risk of VOD. Nonetheless, the effect of exposure on the risk of VOD was notable in both groups of patients regardless of stem cell transplantation status (**Error! Reference source not found.**). After adjusting for the prior stem cell transplantation effect, Cmax of hP67.6 after first dose of GO was still a significant effect on the risk of VOD (p=0.03369).

Since this exposure-response analysis was performed with data from only one dose level (9 mg/m^2), the interpretation of the analysis result should be combined with the limitation of the data. Although the median estimates of the Cmax after first dose of GO at lower dose levels, e.g., 2 or 4 mg/m^2, are

within the range of the individual Cmax levels after first dose of GO at 9 mg/m^2, prediction for the risk of VOD with these lower dose levels is under the assumption that those individuals with low Cmax levels under 9 mg/m^2 can represent the general population under lower doses after adjusting for other covariates. This analysis suggests that the risk of VOD with lower doses is smaller, which is supported by several studies in the literature.

3.6.4.2 Exposure-Efficacy Analyses

Exposure-efficacy relationship, however, was relatively flat (**Error! Reference source not found.**). Among baseline risk factors associated with baseline disease condition, baseline platelet counts, baseline bone marrow blasts, and baseline P-glycoprotein (P-gp) levels were significant predictors for complete remission. Again, this analysis was performed with data obtained from only one dose level (9 mg/m^2). The interpretation of the result should be combined with the limitation of the data. After adjusting for baseline platelet counts, baseline bone marrow blasts, and baseline P-gp, the p-value for the effect of GO exposure on efficacy was 0.605.

This lack of relationship between the exposure and the complete remission was consistent with other exposure measures including AUC after first dose and average AUC. Thus, a substantial loss of therapeutic effect is not expected by reducing dose of GO.

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I concur with the recommendations

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