

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 21174

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Bradley

APR 24 2000

Addendum to NDA Review

NDA 21-174

Submission Date: October 29, 1999

Drug Name: CMA-676 (gemtuzumab ozogamicin, CL-555201)

Primary Reviewer: Lydia Velazquez Kieffer, Pharm.D.

Team Leader: Atiqur Rahman, Ph.D.

A facsimile dated April 12, 2000 sent from the applicant to the Division of New Drug Chemistry I states that approximately 50% of the antibody is not linked to the calicheamicin derivative (please refer to appendix B). The remaining 50% of the antibodies (hP67.6) have about 4 to 6 moles of calicheamicin loaded to every mole of hP67.6. Further confounding the utility of using hP67.6 as the moiety to characterize the pharmacokinetics of CMA-676. The methodology indicates that the assay is not able to differentiate or quantitate the analyte (antibody) in the presence of other constituents (naked antibody, conjugated antibody, or fragments with intact binding sites) in plasma samples. Identification and characterization of conjugated hP67.6 is not possible. Therefore, there is no specificity associated with the assay rendering it of no value for identification and quantitation of conjugated hP67.6 with the active moiety (calicheamicin).

Original review of this NDA relied on the antibody assessment for pharmacokinetic characterization of CMA-676. However, the current package insert only reflects the pharmacokinetics of total and unconjugated calicheamicin because of the non specificity of the antibody assay. The clinical division concurs with the Clinical Pharmacology and Biopharmaceutics decision that the active moiety (calicheamicin) be described pharmacokinetically in the proposed label.

**APPEARS THIS WAY
ON ORIGINAL**

Clinical Pharmacology and Biopharmaceutics NDA Review

NDA 21-174

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Submission Date: October 29, 1999

December 13, 1999

December 23, 1999

January 27, 2000

Drug Name: CMA-676 (gemtuzumab ozogamicin, CL-555201)

Formulation: Intravenous, 5 mg/vial, 0.25 mg/mL conc.

Applicant: Wyeth-Ayerst Research
Philadelphia, PA

Primary Reviewer: Lydia Velazquez Kieffer, Pharm.D.

Pharmacometrics Reviewer: Elena Mishina, Ph.D.

Team Leader: Atiqur Rahman, Ph.D.

Type of Submission: New Drug Application (original)

Category: 1PV

Synopsis: The review evaluates the Clinical Pharmacology and Biopharmaceutics of CMA-676, an antibody-targeted chemotherapy agent. The compound consists of a human engineered anti-CD33 antibody linked to calicheamicin, a cytotoxic antibiotic. The CD-33 antigen is expressed on the surface of leukemic blasts in a high percentage of patients with acute myeloid leukemia (AML). CMA-676 binds to CD33 on the surface of leukemic blasts and is then internalized. Once inside the cell, hydrolysis of the linker takes place which allows calicheamicin to be released and exert its antineoplastic effects. CMA-676 is distributed to leukemia cells that are CD33 positive and hematopoietic cells. About 2 to 3 moles of calicheamicin are available per mole of hP67.6.

The applicant's proposed indication is for the treatment of patients with CD33 positive AML in relapse. The proposed dose is 9 mg/m² given intravenously over 2 hours. The recommended treatment course with CMA-676 is a total of 2 doses with 14 days between the doses.

Twenty-eight studies were submitted to section 6 of the NDA with 24 studies being supportive bioanalytical in nature and 4 studies (one Phase I and three Phase II studies) being clinical trials.

Six assay study reports were submitted that consisted of assay methodology and validation or improvement. The 4 enzyme-linked immunosorbent assay (ELISA) study reports submitted for hP67.6 consistently had specificity as the major problem. The assays can not differentiate

naked antibody, from conjugated antibody, from fragmented antibody; which may be contributing to the variability observed in the pharmacokinetic parameters of hP67.6. The total calicheamicin enzymeimmunoassay (EIA) study report was submitted mainly in summary format, so complete verification was not possible. Variability seems to be the major problem associated with this assay. No deficiencies were noted in the unconjugated calicheamicin ELISA assay report submitted; however, unconjugated calicheamicin concentrations in vivo were close to the lower limit of quantitation (LOQ). Much inherent variability in the assay was observed at the LOQ, possibly contributing to the high variability associated with this moiety's pharmacokinetic parameters.

The antibody portion of CMA-676 (hP67.6) was the moiety characterized pharmacokinetically in a consistent manner across studies. Study 201, 202, and 203 characterized total and unconjugated calicheamicin.

A total of 141 patients were available for non-compartmental pharmacokinetic assessment of hP67.6. Total and unconjugated calicheamicin non-compartmental pharmacokinetic information for 129 patients was available.

Half life of hP67.6 across studies for the proposed dose of 9 mg/m² ranges from 66.5 ± 36.8 hours to 211.4 ± 178.6 hours for dose period one to dose period three. Corresponding AUCs were 132.3 ± 136.3, 243.2 ± 198.2, 173.1 ± 54.7 mg·h/L for dose periods one, two, and three, respectively. Clearance consistently decreased with subsequent dose periods. Course 2 also had an increase in half-life and AUC with an observed decrease in clearance from dose period one to two. C_{max} increased from dose period one to two then decreased in dose period 3 of course one. Course two had a decrease in C_{max} from dose period one to 2.

Total calicheamicin and unconjugated calicheamicin pharmacokinetics had high variability, as was observed with hP67.6. The t_{1/2} (39.0 ± 25.4 versus 62.7 ± 62.8 h) and AUC (2.1 ± 1.8 versus 4.7 ± 4.1 mg·h/L) were statistically significantly different between dose period one and 2 for total calicheamicin. However, corresponding C_{max} was 0.07 ± 0.07 mg/L for dose period one and 0.08 ± 0.03 mg/L for dose period two.

Unconjugated calicheamicin non-compartmental pharmacokinetic analysis revealed an extended t_{1/2} of 221.5 ± 367.7 versus 143.8 ± 177.3 h and a relatively small AUC (0.4 ± 0.4 versus 0.4 ± 0.3 mg·h/L between dose period one and two) when compared to the other two moieties. However, all moieties had relatively high variability.

Excretion and elimination of CMA-676 was characterized in animal studies and is believed to be hepatobiliary in nature. Special Population studies performed include study 203; which is in the geriatric (≥ 60 years of age) population and data from 5 pediatric patients from an ongoing study (study 102). The pediatric study report will be submitted in its entirety at a later time and a full review of the pharmacokinetics in that population will be made then by the Agency. The applicant is not seeking approval in pediatric patients at this time.

Population pharmacokinetics was performed utilizing the data obtained from all four submitted studies (101, 201, 202, and 203). The population analysis is not acceptable due to: poor model predictions, poor evaluation of the difference in clearance between the first and second doses, and the absence of covariate analysis.

COMMENTS

PHASE IV COMMITMENTS

2. Metabolism

The metabolism studies performed in-vitro with liver microsomes and cytosols indicate that numerous metabolites are formed; but specific studies to identify metabolic pathways and isozymes has not been performed. Animal studies indicate that CMA-676 undergoes hepatobiliary elimination making such a study of paramount importance. Additionally, non-linearity has not been ruled-out with CMA-676.

During the treatment phase, 24% of the patients experienced grade 3 or grade 4 bilirubinemia, 5% of the patients experienced grade 3 or grade 4 abnormalities in levels of ALT, and 14% of the patients experienced grade 3 or 4 abnormalities in levels of AST. Thirteen patients had concurrent elevations of transaminases and bilirubin. One patient died with liver failure in the setting of tumor lysis syndrome and multisystem organ failure, another died after an episode of persistent jaundice and hepatosplenomegaly.

As a Phase IV commitment, the applicant will be required to perform the necessary studies to identify which, if any, isozymes are involved in the metabolism of CMA-676 in vivo and identification of any possible active metabolites and their contribution to the total activity of CMA-676.

3. Drug Interaction

Formal drug interaction studies have not been performed. However, as mentioned in the metabolism section above: 1) CMA-676 undergoes extensive metabolism, 2) biliary excretion and gastrointestinal secretion in animal studies was observed, 3) the medical officer's finding regarding hepatotoxicity in a population with normal liver functions upon study entry, 4) Non-linearity issues have not been ruled out, and 5) the Advisory committee's concern regarding hepatotoxicity, all suggests that such studies may be necessary in order to adequately address the possibility of drug interactions with concomitant medications taken by patients.

~~Upon completion of the necessary metabolism studies specified in the metabolism section (number 2 above), depending upon the pathways involved in metabolism, the applicant will be required to perform the necessary drug interaction studies as a Phase IV commitment.~~

4. Pharmacokinetics

Non-compartmental Pharmacokinetic analysis in all the studies (101, 201, 202, and 203)

Total of 142 patients and 275 doses were collected for pharmacokinetic assessment in the original submission for hP67.6 and 38 additional patients were included from the Phase II studies (201, 202, and 203) in the 3-month safety update report dated 27 January, 2000.

Visual inspection of possible covariate correlations was performed in all studies in isolation with no correlations observed; however, the data should have been pooled and a full pharmacokinetic population analysis should have been performed with statistical analysis applied to the pooled data for the evaluation of possible pharmacokinetic parameter correlations with specific covariates. None of the studies had sufficient patient numbers to adequately explore any correlations between pharmacokinetics and pharmacodynamics.

The applicant should pool all the data collected from all trials to explore the possibility of covariate correlations with total and unconjugated calicheamicin pharmacokinetic parameters as a Phase IV commitment.

5. Special Populations

Geriatric Patients

The Advisory Committee voted to approve CMA-676 for the treatment of patients with CD33 positive acute myeloid leukemia in first relapse who are 60 years of age or older. Assessment of the pharmacokinetics for the approved population is not possible at this time.

Please analyze all pharmacokinetic data for total and unconjugated calicheamicin for patients 60 years of age or older separate from younger patients. This analysis will provide pharmacokinetic parameter comparison between patients under 60 years and patients that are 60 years of age or older. Submit your analysis to the Agency to update the Clinical Pharmacology section of the package insert as a Phase IV commitment.

GENERAL COMMENTS

Pharmacometrics Comments:

1. The applicant explained the different steps of population pharmacokinetic model building and choosing the optimal model to fit the data based on model diagnostics. Final model CMA016 to describe the pharmacokinetics of hP67.6 was two-compartmental model with inter-individual error terms on clearance and volume of distribution and estimation of the additive and proportional residual errors as population parameters. The graphic diagnostics of the final model verified by the Agency showed that it is not optimal. It predicts higher than observed plasma concentrations at low concentrations, and lower than observed plasma concentrations at high concentrations. Although the applicant commented that six patients had very different from the rest of the population parameter estimations, this alone cannot explain the poor fit of the model. The applicant should attempt to optimize the model and submit the results to the Agency for review.
2. The decrease in clearance after the second dose was estimated about 20% of the clearance after the first dose and may be considered clinically irrelevant. However, in the study reports 0903B1-201 and 0903B1-203, the differences in clearance after the first and second dose were above 2 fold, which accounts for approximately half of all studied patients. Patients with this difference in the exposure may be the candidates for dose adjustment. Therefore, the differences in the observed clearance between the first and second dose in the referred studies are not in agreement with the 20% difference in the population clearance values predicted by the model. The Agency recommends that the applicant re-evaluate the influence of the second dose on the clearance by the population modeling.
3. The applicant tested the influence of the demographic covariates on the pharmacokinetic parameters (clearance and volume) based on the visual comparison of the plots of examined parameters. Since gemtuzumab zogamicin is recommended in the narrow patients' population of 60 years of age and older, the applicant is recommended to statistically evaluate the influence of age as a covariate. The applicant should incorporate age as a covariate into the equation for the fixed effect parameters using NONMEM.

4. The applicant is recommended to statistically evaluate the hepatic function as a covariate since gemtuzumab zogamicin is extensively metabolized, excreted by liver and bile, and has a substantial hepatic toxicity.

Bioanalytical Assay Comments:

Study 32597 – Laboratory tests performed for the CMA-676 101 study

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commercial

information

Labeling Comments

RECOMMENDATIONS:

The applicant is requested to agree to the following Phase IV commitments to address the deficiency of the NDA 21-174 submission based on the above comments from the Clinical Pharmacology and Biopharmaceutics perspective.

1. You are recommended to improve the assay for total and unconjugated calicheamicin. Using the improved assay, please characterize the pharmacokinetics of CMA-676 in the clinical trial that you will conduct to fulfill the condition for the accelerated approval of the drug. You may also conduct a separate clinical study to characterize the pharmacokinetics of CMA-676.
2. The applicant will be required to perform the necessary studies to identify which, if any, isozymes are involved in the metabolism of CMA-676 in vivo and identification of any possible active metabolites and their contribution to the total activity of CMA-676.
3. Upon completion of the necessary metabolism studies specified in the metabolism section and depending upon the pathways involved in metabolism, the applicant will be required to perform the necessary drug interaction studies.
4. Please analyze all pharmacokinetic data for total and unconjugated calicheamicin for patients 60 years of age or older separate from younger patients. This analysis will provide pharmacokinetic parameter comparison between patients under 60 years and patients that are 60 years of age or older. Submit your analysis to the Agency to update the Clinical Pharmacology section of the package insert.
5. The applicant should pool all the data collected from all trials to explore the possibility of covariate correlations (age, weight, hepatic toxicity, responders versus non-responders for pharmacokinetic variability reduction, race, gender, etc.) with total and unconjugated calicheamicin pharmacokinetic parameters.

// 4-21-00
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Lydia Velazquez Kieffer, Pharm.D.
Reviewer
Division of Pharmaceutical Evaluation I

151 4/24/00
Atiqur Rahman, PhD.
Team Leader
Division of Pharmaceutical Evaluation I

cc: Orig NDA
HFD-150/ Division File
HFD-150/ SBradley, JBeitz, PBross, XChen, EDuffy, RSandip, PAndrews
HFD-860/ MMehta, ARahman, LVelazquezKieffer
HFD-340/Vishwanathan

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW OF
NDA 21-174: Mylotarg® (gemtuzumab zogamicin)**

APPLICANT: Wyeth-Ayerst

Reviewing Clinical Pharmacology and Biopharmaceutics Officer:

Lydia Velazquez Kieffer, Pharm.D.

ODAC MEETING: March 17, 2000

Table of Contents

Synopsis	1
Comments – Phase IV Commitments	3
Assays and Bioanalytical Reports	3
Metabolism	3
Drug Interaction	4
Pharmacokinetics	4
Special Populations	5
General Comments	5
Pharmacometrics Comments	5
Bioanalytical Assay Comments.	6
Labeling Comments	7
Recommendations	10
Table of Contents	11
Question Based Review	12
Assays	12
Metabolism	12
Drug Interactions	13
Pharmacokinetics	14
Special Populations	15
Primary Reviewer's Detailed Review	16
Pharmacometrics Review	29
Appendix A – Label	

QUESTION BASED REVIEW:

Assays

Was an adequate assay developed for detection and identification of all the moieties (hP67.6 conjugated antibody, unconjugated calicheamicin, and conjugated calicheamicin) chosen by the applicant to characterize pharmacokinetically in all submitted studies?

All assays methods developed for the three moieties of CMA-676 were ELISA.

hP67.6 Assay - Calibration Range of _____ ng/mL

The ELISA assay developed for hP67.6 had an inherent problem upon evaluation (study reports 29884, 32629, 34356, 35312, and 35313).

Much of the report was submitted in summary format making verification of the conclusions made by the applicant not possible. However, upon evaluation of the submitted summary, specificity seems to be the major problem associated with the methodology for identification and quantitation of conjugated hP67.6. The assay developed for this moiety can not distinguish naked antibody from conjugated antibody or antibody fragments with intact binding sites.

Identification and characterization of conjugated hP67.6 is not possible due to lack of specificity with the assay. As a result, the assay has no value in this setting.

Unconjugated calicheamicin - An assay was developed for the quantitation of unconjugated calicheamicin with an analytical range of _____ ng/mL. However, plasma concentrations of unconjugated calicheamicin were low and close to the lower limit of quantitation (LOQ) possibly contributing to the high variability observed. Additionally, concentrations were measured for a relatively short period of time; which may have also contributed to the variability observed.

Total calicheamicin analytical range for the assay is _____ ng/mL. However, much variability was observed as well. This study report was submitted in summary format, making verification of the methodology not possible.

All three moieties' assays involved some kind of ELISA methodology in their development. One of the weaknesses of the ELISA method is lack of specificity. ELISA may not be the optimal way of identifying and quantitating total and unconjugated calicheamicin.

Metabolism

Was sufficient metabolism characterization performed to identify metabolic pathways and corresponding isozymes?

The metabolism studies performed in-vitro with liver microsomes, cytosoles, and HL-60 promyelocytic leukemia cells indicate that numerous metabolites are formed. Hydrolysis, oxidation and reduction of the disulfide bond were observed. In summary, 11 metabolites of NAc-gamma calicheamicin DMH were found after incubation in human liver microsomes and cytosol. The biotransformation pathways identified in microsomes were oxygenation 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. Some metabolites were found in both liver and leukemia cell preparations, suggesting that the metabolism of the calicheamicin derivatives may not be cell specific. The detection of NAc-epsilon calicheamicin and its derivatives in cells may indicate that the reactive diradical species of NAc-epsilon calicheamicin may be formed via a glutathione-dependent reduction of the disulfide bond of NAc-gamma calicheamicin DMH within cells.

However, specific studies to identify metabolic pathways and isozymes has not been performed. Animal studies indicate that CMA-676 undergoes hepatobiliary elimination making such a study of paramount importance. Additionally, non-linearity has not been ruled-out with CMA-676.

Additional information on the metabolic pathway and isozymes was requested following the 45-day filing meeting via telecon on December 17th, 1999. The applicant stated that they have not identified any of the metabolic pathways with isozymes at this time (applicant's response dated December 23, 1999 is in appendix C). Urine samples are being collected in study 203; but results of those analysis have not been received.

~~Appropriate metabolism information including activity of the metabolites has not been~~ submitted in order for the Agency to assess the necessary and appropriate drug interaction studies and their possible impact on safety. On December 17th, 1999 (post 45-day filing meeting) we also requested additional information regarding which metabolites are believed to be active. That information is not known at this time because the necessary studies have not been performed.

During the treatment phase, 24% of the patients experienced grade 3 or grade 4 bilirubinemia, 5% of the patients experienced grade 3 or grade 4 abnormalities in levels of ALT, and 14% of the patients experienced grade 3 or 4 abnormalities in levels of AST. Thirteen patients had concurrent elevations of transaminases and bilirubin. One patient died with liver failure in the setting of tumor lysis syndrome and multisystem organ failure, another died after an episode of persistent jaundice and hepatosplenomegaly.

During the Advisory Committee deliberations, hepatotoxicity was a concern expressed by the Committee members.

Drug Interaction Study

Were any formal drug interaction studies performed and are they necessary?

No formal drug interaction studies have been performed. However, 1) CMA-676 undergoes extensive metabolism as mentioned in the metabolism section, 2) biliary excretion and gastrointestinal secretion in animal studies was observed, 3) the medical officer's findings

revealed that hepatotoxicity was taking place in patients with normal liver functions upon study entry, 4) non-linearity issues have not been ruled out, and 5) the Advisory committee's concern regarding hepatotoxicity, all suggests that appropriate drug interaction studies may be necessary in order to adequately address this possibility taking place with concomitant medications that may be taken by patients.

Pharmacokinetics

Were the pharmacokinetics of CMA-676 adequately characterized across studies?

Non-compartmental pharmacokinetics were performed in all 4 studies submitted. All the Phase II studies submitted were ongoing at the time the NDA was submitted. Additional pharmacokinetic data was submitted later in the 3-month safety update report for all three Phase II studies. The information submitted included pharmacokinetic data for 38 additional patients for the hP67.6 pharmacokinetic analysis and data on 70 additional patients for the calicheamicin pharmacokinetics update. hP67.6, total and unconjugated calicheamicin was characterized pharmacokinetically in all three Phase II studies. Study 101 characterized the hP67.6 only. An increase in C_{max} , AUC, and half-life was observed between dose period one and two in a consistent manner. Corresponding decreases in clearance and volume of distribution was observed as well.

Additionally, variability in the pharmacokinetic parameters was observed to be as high as 100% across all four clinical trials submitted in a consistent manner. The applicant claims that the variability observed may be due to a tumor burden load decrease from dose period one to dose period two. Since calicheamicin is cleared intracellularly, less tumor load during dose period two may translate to a decrease in clearance. Other factors that may be contributing to the variability observed may be due to a possible decrease in bone marrow reserve due to depletion from chemotherapy from previous courses/treatments. The non specificity of the assays that were developed for the hP67.6, unconjugated calicheamicin, and total calicheamicin may be confounding results as well and contributing to the high variability. Detectable hP67.6 levels were observed in the Phase I trial (study 101) prior to the next dose being administered (14 days after the administration of dose one); which may account for the increase in C_{max} observed and the corresponding changes in the pharmacokinetic parameters observed between dose period one and dose period two. All three moieties had an extended half-life during dose period one (66.53 ± 36.82 hours for hP67.6, 39.02 ± 25.39 hours for total calicheamicin, and 221.45 ± 367.72 hours for unconjugated calicheamicin) for studies 201, 202, and 203; which may be contributing to the disparity in concentrations and pharmacokinetics observed.

Non-linearity could not be ruled out when study 101 data was examined; however due to small patient numbers and high variability in the pharmacokinetics of the hP67.6, no conclusions can be made at this time whether this could also be a contributing factor.

Adequate characterization of all three moieties was not possible due to the high variability observed across studies.

Does the 3-month pharmacokinetic data submitted with the safety update allow for complete validation of the information submitted?

A total of 142 patients and 275 doses were collected for non-compartmental pharmacokinetic assessment in the original submission for hP67.6 and 38 additional patients were included from the Phase II studies (201, 202, and 203) in the 3-month safety update report dated 27 January, 2000.

The original submission had total and unconjugated calicheamicin pharmacokinetic information for 56 patients. The 3-month safety update has a summary table for 129 patients. However, the applicant did not provide CL, V_d for total and unconjugated calicheamicin in the original submission for study 201 or in the 3-month update of studies 201, 202, and 203.

As a result, complete validation of all data submitted with the 3-month safety update was not possible.

Was the non-compartmental pharmacokinetic analysis in all the studies (101, 201, 202, and 203) submitted performed in a manner that will allow true assessment of the pharmacokinetics of CMA-676 and the covariates analyzed?

Visual covariate testing was performed in all studies in isolation with no correlations observed. However, the data should have been pooled and a full pharmacokinetic population analysis should have been performed with statistical analysis applied to the pooled data for the evaluation of possible pharmacokinetic parameter correlations with specific covariates. None of the studies had sufficient patient numbers to explore any correlations between pharmacokinetics and pharmacodynamics adequately.

Special Populations

Were specific populations of concern appropriately characterized?

Hepatic

No formal study was performed in the hepatically impaired population.

As stated in the proposed label, during the treatment phase, 24% of the patients experienced grade 3 or grade 4 bilirubinemia, 5% of the patients experienced grade 3 or grade 4 abnormalities in levels of ALT, and 14% of the patients experienced grade 3 or 4 abnormalities in levels of AST. Thirteen patients had concurrent elevations of transaminases and bilirubin. One patient died with liver failure in the setting of tumor lysis syndrome and multisystem organ failure, another died after an episode of persistent jaundice and hepatosplenomegaly.

During the Advisory Committee deliberations, hepatotoxicity was a concern that was discussed. Performing a study in the hepatically impaired population with CMA-676 would be unethical due to the observation of hepatotoxicity occurring in study patients that had normal liver functions upon study entry.

Hepatic impairment was not appropriately characterized or addressed by the applicant.

Pediatric

A formal pediatric study is ongoing with only five patient's data submitted at this time. The applicant is not requesting approval in this population at this time. A full review will be performed upon submission of all results from this study.

Geriatric

Pharmacokinetic characterization was performed with the hP67.6 and the same high variability in the pharmacokinetic parameters was observed as in studies 101, 201, and 202. Upon submission of the 3-month safety update, additional pharmacokinetic data characterizing total and unconjugated calicheamicin was summarized with study 201 and 202. Full evaluation of the pharmacokinetics in the approved population is not possible at this time due to the manner in which the data was submitted.

The Advisory Committee recommended approval in this subgroup of patients (*60 years of age or older*) with relapsed acute leukemia.

PRIMARY REVIEWER'S DETAILED REVIEW:

Assays and Bioanalytical Reports

32598: Flow Cytometry for CMA-676 101 Study. This method was used to quantitate levels of CD33 on AML leukemic blast cells for CMA-676. The quantitative data was used to define the CD33 expression parameters for possible use in further studies based on preliminary results in this study.

Study 29884 entitled: "CMA-676: Validation of an ELISA for quantitation of antibody (hP67.6) in human plasma." Presented in study 101 supportive studies.

Method and Validation Summary:

ELISA: ~~ELISA method for antibody in human plasma developed in Dept. 975 of Medical Research Division.~~

Method of Calculation: 6-Parameter Logistic Model run by MAINELISA program on RS 6000

Matrix, Volume: Pooled human plasma in EDTA, 0.1 mL

Compound: hP67.6-conjugate (CL555,201)

Assay Standard: CL555,201, Batch#4489A24-102593-R1592-24

LOQ: 7 ng/mL

Calibration Range: 7 to 100 ng/mL

Specificity: Assay doesn't distinguish between naked antibody, conjugated antibody, or fragments with intact binding

Precision and Accuracy: Based on Q.C. Samples, %CV is 1.5% to 23.3%, %Error is - 11.6% to 35.3%

Freeze/Thaw effects: No effects were observed up to three freeze/thaw cycles.

Stability: Q.C. samples are stable up to two months @-70°C. Long term study is ongoing.

Inter-day variation: Based on Q.C. Samples, %CV is 5.8%

Matrix effects: No matrix effects were observed with 4 separate pools of human plasma.

1. A summary was submitted with no raw data provided. Therefore, verification of most of the conclusions made by the applicant regarding the assay is not possible.
2. The reference standards documented purity has not been stated. The batch number of the standard (hP67.6 conjugate) is stated with no additional information. The antibody portion of the conjugate is a human IgG4 specific for human CD33 antigen. The applicant states that this is the appropriate standard for the assay because it is the molecule to be analyzed in the course of the study; but no further information is stated on the selection process or purity of the standard.
3. The assay is not able to differentiate or quantitate the analyte (antibody) in the presence of other constituents (naked antibody, conjugated antibody, or fragments with intact binding sites) in the sample. Therefore, there is no specificity with the assay. The assay is of no value for the purposes being used.
4. No information was provided on the selection process of the LOQ based on the guidance entitled: "Bioanalytical Methods Validation for Human Studies" dated 12/14/98.
5. Linearity: Information on deviation from the LOQ or standards other than LOQ from nominal concentrations was not provided. However, the applicant states that the correlation coefficient was 0.99968
6. Accuracy: The mean value of the LOQ should not deviate by more than 20% according to the guidance. However, no data were provided for the LOQ with this assay method. Please refer to their method and validation summary above.
7. Precision: The LOQ should not exceed a coefficient of variation (CV) of 20%; which is not verifiable because no data were submitted for the LOQ. See the method and validation summary above.
8. Freeze/Thaw Stability: At least three aliquots at each of the low and high concentrations should be analyzed for stability according to the guidance. However, only 2 aliquots of the high concentration data was provided.
9. Long term stability testing is ongoing and is reported in a later report.
10. Stability testing for stock solution were not provided.

11. Sensitivity: According to the guidance, the lowest standard (1 ng/mL) should be accepted as the LOQ of the method if the between-batch CV at the LOQ is $\leq 20\%$. In this summary, the LOQ failed; but no data were presented on the chosen LOQ of 7 ng/mL.

Study 32629 entitled: **"CMA-676: Additional validation of an enzyme-linked immunosorbent assay for quantitation of hP67.6 antibody in human plasma.** No mention is made that validation took place across studies for studies 101, 201, 202, and 203.

1. The nominal and concentration ranges varied with the test performed. It remains unclear why this took place.
2. When the extended assay range was studied, the lower concentrations were not analyzed again in order to be able to compare previous results with current analyses and determine if same variability exists.
3. An internal standard does not seem to have been used for this re-analysis.
4. Long-term stability: According to the guidance long-term stability should be determined by storing at least three aliquots of each of the low and high concentrations under the same conditions as the study samples. It seems only one concentration was tested (50 ng/mL); which was neither the low or high concentration.
5. Only the 3 highest concentrations (1000, 2000, and 4000 ng/mL) were tested for the refrigerated storage stability test. The raw data for the fresh samples was not provided for verification. Rationale for the selection of a 7 day waiting period for quality control purposes was not provided.
6. Room temperature storage stability testing of CMA-676 in human plasma does not have the low concentration analysis. Rationale for choosing 6 hours as the analysis time was not provided.
7. The accuracy and precision for the extended assay range of CMA-676 in human plasma should have contained the lower concentrations used previously as a baseline to truly measure the disparity observed previously in study 29884.
8. The inter-day precision and accuracy for the determination of CMA-676 in human plasma did not use the Low and highest concentrations (1 ng/mL and 4000 ng/mL, respectively).
9. The Low and high concentrations for the matrix effect for the determination of CMA-676 in human plasma was not used with no rationale provided for their omission.

Study 32628 entitled: **"CMA-676: A phase I study of human anti-CD-33 monoclonal antibody (hP67.6 antibody) - calicheamicin drug conjugate (hP67.6 conjugate) as**

treatment for patients with Acute Myeloid Leukemia (AML): bioanalytical report. To determine if an immune response had been elicited in patients after CMA-676 administration, patient plasma samples were evaluated. Immune response evaluation was based on the formation of anti-hP67.6 antibodies and the formation of anti-calicheamicin derivative (anti-Nac-gamma calicheamicin DMH AcBut) antibodies. All evaluations were performed by ELISA methods and were developed only to identify a positive or a negative response. This report summarizes the plasma concentration and immune response data of patients enrolled in this study. This study report was evaluated by CBER. Please refer to Appendix D.

Study 34358 entitled: Additional Bioanalytical Data. This is a refined assay version of the ELISA used in support of GTR-32628. This analysis was performed for study 101 only. The possible occurrence of antibodies to hP67.6 antibody and to Nac-gamma calicheamicin DMH AcBut in patients' plasma was monitored on days 7, 14, 21, and/or 28 after each treatment. This study report was evaluated by CBER.

Study 34356 entitled: CMA-676: Validation of a refined enzyme-linked immunosorbent assay for quantitation of hP67.6 antibody in human plasma. This assay was used for studies 201, 202, and 203. Cross validation data was not provided, possibly not performed. The initial validation results of the ELISA for determination of plasma concentration of hP67.6 antibody were presented in GTR-29884 and GTR-32629. The previously reported method used a number of dilution schemes such that the percentage of plasma in the final sample was variable; which could result in a matrix effect that produced a negative bias in the ELISA. The reported assay accuracy ranged from []% bias and the lower limit of quantitation was not established. In the refined ELISA procedure, diluted plasma samples contained 20% plasma.

1. The within-run (intra-day) and between-run (inter-day) precision and accuracy did not include the LLOQ or the ULOQ. No rationale was provided for the choices of concentrations used.
2. Results of the dilutional linearity analysis for determination of hP67.6 antibody concentration after spiking CMA-676 in human plasma indicate that a CV was not provided and the highest concentration was not used. Two of the five standards did not meet the factors necessary for developing a calibration curve.
3. Results of the determination of hP67.6 antibody concentrations in the blinded CMA-676 plasma samples analysis indicate that 44% (11/25) of the non-zero blinded samples had measured hP67.6 antibody concentrations with assay biases greater than 20% from the nominal concentration. This may be an indication that the refined assay may still have the same inherent problems that the original assay had possibly due to a matrix effect, as the applicant has stated or possibly due to the inability of the assay to distinguish naked antibody from fragmented, and conjugated antibody.

Study 35312 entitled: A study of the efficacy and safety of CMA-676 as single agent treatment of patients with acute myelogenous leukemia in first relapse (protocol 201): Bioanalytical report on plasma concentrations of hP67.6 antibody. This assay was used for study 201. The high concentration QC plates indicate that the %CV exceeded 20% (actual value 37.3%) possibly explaining the high variability observed in C_{max} . This may be an indication that the methodology requires further development.

Study 33976 entitled: Validation of an ELISA method for determination of unconjugated calicheamicin in human plasma. This assay was used for studies 201, 202, and 203. The analytical range for the assay is [] ng/mL.

Plasma concentrations were low throughout the assay and close to the LOQ and unconjugated calicheamicin could be measured only for a short period of time. Both these shortcomings may possibly be contributing to the variability observed.

Study 33977 entitled: Validation of an EIA method for determination of total calicheamicin in human plasma. This assay was used for studies 201, 202, and 203. The analytical range for the assay is [] ng/mL. However, the limit of quantitation for the assay was changed from [] ng/mL. This change was received with the 3-month safety update submitted on January 27, 2000 with no attached data or rationale for such change.

1. In the freeze/thaw stability tests results, determination of the high and low limits was not provided. The calculations for mean, SD, %CV, and % difference from theoretical was not given.
2. The applicant did not provide room temperature stability calculations for SD, %CV, and %difference from theoretical for verification.
3. The matrix interference data was not provided for verification.
4. Total calicheamicin recovery data for verification was not provided.
5. Dilutional parallelism data for verification was not provided.

34616: Determination of conjugated and unconjugated calicheamicin in human plasma samples from protocol 201-US entitled 'A study of the efficacy and safety of CMA-676 as single agent treatment of patients with acute myeloid leukemia in first relapse'.

ELISA analysis of conjugated calicheamicin in human EDTA plasma.

1. The inter-assay precision and accuracy quality control samples indicate that the lower concentration QC sample is >20% CV possibly due to the methodology that may require further development in order to obtain reproducible results throughout assay utilization.

Study 37934 - Flow cytometry (immunophenotyping) for CMA-676 201 Study.

Correlation of the data obtained from this study to remission status could not be made.

37938, 37939, and 37940: CD33 Site saturation, MDR efflux, and in-vitro inhibition for CMA-676 201, 202, and 203 study.

1. The amount of Pgp on the surface of these cells was not provided.
2. The function of Pgp cells in this particular situation is unclear.
3. The amount of antibody-drug conjugate that binds to CD33 cells remains unclear.

36823, 36824, 38010, and 38011: Interim bioanalytical report on incidence of antibodies to hP67.6 antibody and to Nac-GAMMA calicheamicin DMH AcBUT in patient plasma. Has been reviewed by CBER.

35313: Bioanalytical report of study 202-EU on plasma concentrations of hP67.6 antibody.
No comments.

37936 and 37937: Flow cytometry (immunophenotyping) and CD33 site saturation for CMA-676 202 and 203 study.

Almost complete saturation was observed in the 6 hour post CMA-676 administration samples indicating that upon infusion of CMA-676 saturation of CD33 antigenic sites occurs. Correlation of these data with remission status was not possible.

35313: Interim bioanalytical report on plasma concentrations of hP67.6 antibody for study 203.

The analytical performance of the ELISA during the QC sample analysis of protocol 203 indicates that the high concentration sample had a %CV of 23.7 and 16.6 for 1998 and 1999, respectively. This may be due to the reproducibility of the assay; which may indicate that the methodology is not fully validated and requires further improvement.

Study 37935 - Flow cytometry (immunophenotyping) for CMA-676 203 Study.

Correlation of the data obtained from this study to remission status could not be made.

Bioequivalence

The applicant is requesting a waiver from conducting a human bioequivalence study of material reconstituted in the presence or absence of Human Serum Albumin (HSA) due to:

- 1) CMA-676 pharmacokinetic variability can be as much as 100%.

- 2) CMA-676 concentration and pharmacokinetics is remarkably different between dose period 1 and 2; which the applicant claims is due to the decrease in tumor burden load.
- 3) HSA represents approximately 3 to 4 % of the final solution.

Drug Interaction Studies

No formal drug interaction studies have been performed. A visual inspection of the pharmacokinetic parameters of hP67.6 and demographic, safety and efficacy covariates were made within each study with no correlations found. No statistical evaluation was made in any of the Phase II studies.

Summary of submitted studies:

Phase I (101) US (Vol 50) – CD33+ patients with AML

- Used 2 concentrations of CMA-676 (2.5 and 5 mg/vial) formulation changes made do not seem to be significant (Volume 2 pg 144)
- CMA-676 dose linearity could not be determined due to: LMOQ constraints, large interpatient variability, small number of patients in each treatment group, few patients received different doses, and the applicant not capturing 3 half-lives in their sampling scheme.
- hP67.6 was assayed in this study and the assay is not able to detect naked antibody from conjugated antibody or antibody fragments.
- Samples were collected for calicheamicin concentrations; but were not measured because of assay problems and limited sample stability.
- All patients received 650 mg of acetaminophen (PO) and 25 to 50 mg of diphenhydramine (IV) 15 to 30 minutes before CMA-676 administration.
- Blood sampling for pharmacokinetic assessment was performed out to 96 hours, 2 half-lives at best.
- The maximum tolerated dose (MTD) was never reached and the dose limiting toxicity (DLT) was not fully identified. However, dose escalation was stopped at 9 mg/m² because the hematologic toxicity encountered was considered to be clinically important and 4/7 patients had clearance of their blast cells from their bone marrow. Evaluation of the CD33 saturation data led to the conclusion that this dose level effectively saturated the CD33 sites regardless of the leukemia burden.
- Some type of pharmacokinetic saturation process may be taking place at the 1 to 2 mg/m² dose level as evidenced by AUC. Dose period one was not separated from dose period two making assessment of the data difficult.
- Detectable drug levels were observed in some patients between the first and second dose or even the third dose in some patients. This may account for the intrapatient increase in drug concentrations observed between dose periods and possibly the changes in pharmacokinetics observed due to drug not being completely cleared and eliminated by the leukemic and hematopoietic cells; possible drug accumulation may be taking place.

- A new cell line was used in study 101 for 4 patients; however the same amount of calicheamicin was used. C_{max} for hP67.6 was the only pharmacokinetic parameter used to determine if there were any differences in the pharmacokinetics between the two cell lines as demonstrated in a graph. No other analysis seems to have been made.
- No formal pharmacokinetic/pharmacodynamic analysis was performed other than a graph to demonstrate that as AUC increased, %CD33 saturation increased as well in peripheral and bone marrow blasts cells.
- Age and gender differences were analyzed retrospectively to CMA-676 CI at the 9 mg/m² dose with no relationship observed. These two observations were made visually by plotting the covariates graphically. Further analysis was not performed and dose period analysis was not addressed.

non-compartmental pharmacokinetics demonstrated:

- AUC↑ with dose↑ - possible non-linearity may be taking place; but the applicant didn't present data from dose period 1 versus 2 (they added everything together). Adding dose periods has confounded the data and assessment of non-linearity is not possible.
- CL↓ with dose↑ possibly due to more drug than tumor burden within the same cycle or possibly due to non-linearity. Variability is as high as 100% across doses.
- V_{ss} ↓ with dose↑. Variability is between about 30 and 100% across doses.
- Half-life seems to increase slightly with increase in doses. Variability is between 9 and 95% across doses.
- ~~There are more number of doses than number of patients within each dose level~~ indicating that more than 1 dose was administered to some patients within each dose level.

Phase II (201) US/CA (Vol 54)– AML

- Concentrations of 5 mg/vial was used throughout study
- We requested that sampling be extended beyond 96hours and the applicant did so.
- Concentrations of unconjugated calicheamicin were very low possibly adding to the variability observed.
- A significant difference in pharmacokinetic parameters were observed between dose period 1 and 2 for hP67.6; similar to study 101. In study 101 a carry-over effect may have been occurring due to detectable drug concentrations observed at the beginning of the next dose period and the reduction of tumor burden. This same phenomenon may be taking place here; thus accounting for the increase in C_{max} , $t_{1/2}$, and AUC with a corresponding decrease in CL, and V_{ss} . Variability in the pharmacokinetic parameters was as high as 100%.
- Total calicheamicin – the applicant did not provide CL, V_{ss} , or V_z . The applicant stated that it was not applicable with no further explanation. Variability is almost 100%. Half-life increases from dose period 1 to 2 and 3; however AUC increase from dose period 1 to 2 then drops in dose period three.

- Unconjugated calicheamicin – the applicant did not provide CL, V_{ss} , or V_z and stated that it was not applicable with no further explanation. Half-life increases from dose period 1 to 2 and 3; however AUC remains fairly constant as does C_{max} .
- A significant difference in pharmacokinetic parameters were observed between dose period 1 and 2 for total and unconjugated calicheamicin with variability close to 100%; similar to what was observed for the hP67.6 moiety.
- The ratio of total or unconjugated calicheamicin to hP67.6 AUC was not 1 to 1 in either dose period. Total and unconjugated calicheamicin AUCs were very low compared to the AUC of hP67.6; however, the assay for hP67.6 has no specificity inflating the AUC for hP67.6.
- Covariates that were assessed with pharmacokinetic parameters include elevated liver enzymes (not bilirubin) with first dose AUC for hP67.6 with no correlation found. However, dose period 1 to 2 should have been assessed for all patients to see if pharmacokinetic parameters like CL, AUC, half-life, etc. could be correlated with adverse events in dose period 1 compared to 2.
- Calicheamicin and hP67.6 concentrations decreased in a parallel fashion indicating to the applicant that the molecule remains intact. It's difficult to come to such a conclusion solely due to this graphical observation, especially since the assay for the hP67.6 has no specificity. At certain time points, we may just be looking at fragmented hP67.6. As a result, we are uncertain what's being followed when we look at a concentration versus time plot of hP67.6.
- Variability seemed higher in dose period 2 for hP67.6 pharmacokinetic parameters possibly due to remaining fragments of antibody post infusion from dose period 1. Since the assay has no specificity, this could further confound what is being assessed pharmacokinetically. However, a consistent change in pharmacokinetics is observed between dose periods.
- Evaluation of a possible relationship between the first dose of hP67.6 AUC and race was made with no correlations found; however, there were not enough patients from the other races observed (black, Asian, other) to make any definitive conclusions. A better approach would be to pool all data from studies 101, 201, 202, and 203 and perform a population analysis in order to assess on a preliminary basis if any correlations can be seen between various covariates (age, gender, weight, BSA, race, etc) and the pharmacokinetic parameters for total and unconjugated calicheamicin.
- **Phase II (202) EU (Vol 63/1) – AML**
 - Same concentration of 5 mg/vial was used throughout study
 - No significant differences in the pharmacokinetics of hP67.6 was observed between the 1st and 2nd dose periods from preliminary data sent with original submission. However, variability was very high possibly confounding any statistical conclusions
 - hP67.6 C_{max} was greater in cycle 2
 - No conclusions can be made regarding hP67.6 AUC and ethnic origin because of the limited number of patients enrolled in the black category.
- **Phase II (203) EU/US (Vol 67/1) – AML**
 - Same concentration used throughout (5mg/vial) study

- Study was conducted in an older population (60 to 84 years, mean 70 years)
- Statistically significant differences observed between dose period 1 and 2 in hP67.6 AUC from preliminary data sent with original submission
- As in previous studies, no pharmacokinetic/pharmacodynamic correlations were observed. However, patient numbers were small and the correlations were made by visual inspection.

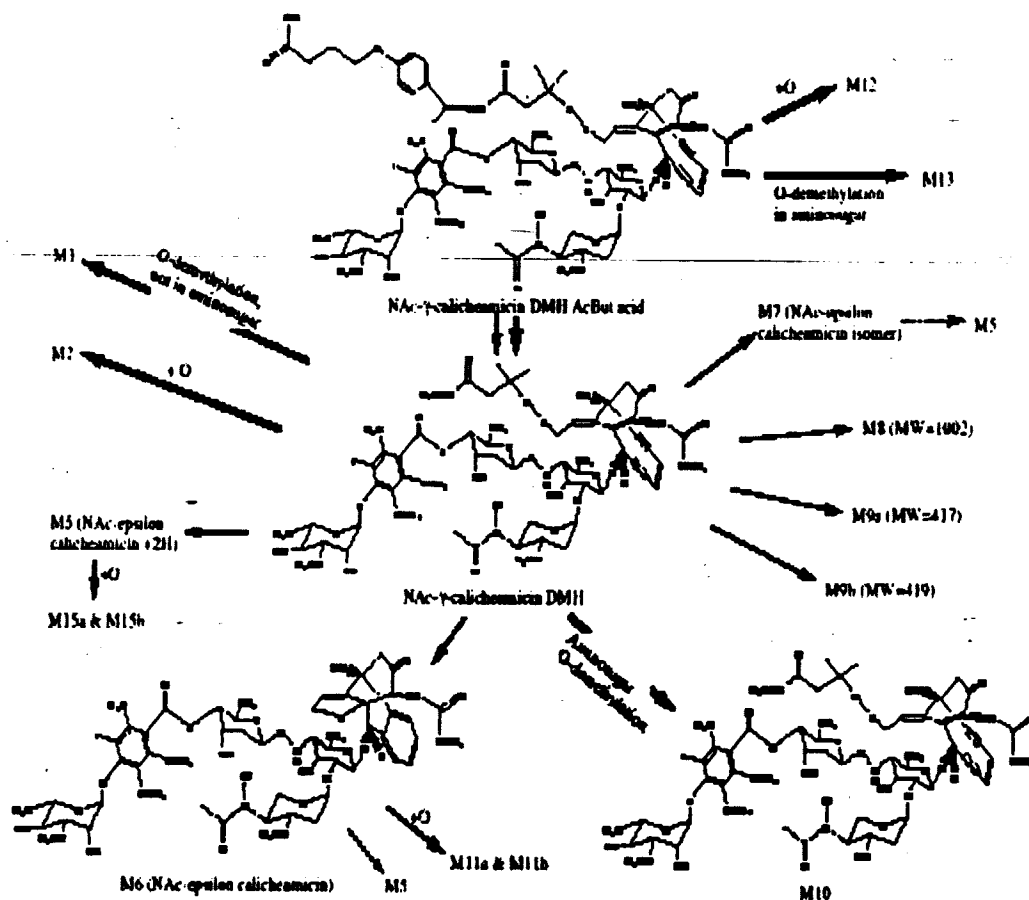
Overall pharmacokinetic assessment from non-compartmental pharmacokinetic analysis in all the studies (101, 201, 202, and 203)

- Total of 142 patients and 275 doses were collected for pharmacokinetic assessment in the original submission for hP67.6 and 38 additional patients were included from the Phase II studies (201, 202, and 203) in the 3-month safety update report dated 27 January, 2000.
 - The original submission had total and unconjugated calicheamicin pharmacokinetic information for 56 patients. The 3-month safety update has a summary table for 129 patients.
 - The applicant did not provide CL or V_d information for total and unconjugated calicheamicin in the original submission for study 201 or in the 3-month update of studies 201, 202, and 203. No explanation was provided for the omission of such data.
 - Covariate testing was performed in all studies visually with no correlations observed between pharmacokinetic/pharmacodynamic parameters. However, the data should have been pooled and a full pharmacokinetic population analysis should have been performed with statistical analysis applied to the pooled data for the evaluation of possible pharmacokinetic parameter correlations with specific covariates. None of the studies had sufficient patient numbers to explore any correlations between pharmacokinetic and pharmacodynamics.
-
- **Study (Phase I study)** – Data in 5 pediatric patients has been submitted in the 3-month safety update with ages not specified at this time. The dose being administered to this population will be in the range of 6 mg/m² to 12 mg/m². A summary pharmacokinetic table with 5 patients was submitted with the 3-month safety update. Consistent differences in the pharmacokinetics from dose period 1 to 2 seem to be occurring, as in the adult data. However, larger patient numbers and more detailed patient information will be necessary in order to adequately assess this population.
 - **Population Pharmacokinetics with 101, 201, 202, and 203 studies** – Please refer to attached review by the pharmacometrics consultant.

Metabolism

- In vitro studies were conducted to examine the metabolism of NAc-gamma calicheamicin DMH AcBut in human liver microsomes and cytosol. The proposed metabolic pathway is shown in Figure 2.
- NAc-gamma calicheamicin DMH AcBut was hydrolyzed rapidly and extensively to NAc-gamma calicheamicin DMH in microsomes but to a lesser extent in cytosol. Five metabolites (M1, M2, M10, M12, and M13) were found as microsomal metabolites; they were oxygenated and demethylated metabolites. Metabolites M1, M2, and M10 were also detected as microsomal metabolites of NAc-gamma calicheamicin DMH.

FIGURE 2. PROPOSED METABOLIC PATHWAY OF NAc-GAMMA CALICHEAMICIN DMH AcBut IN HUMAN LIVER MICROSOMES (⇨) AND CYTOSOL (→)



- In cytosol, metabolites M5, M6, M7, M8, M9a, M9b, M11a, M11b, M15a, and M15b were found following incubation with NAc-gamma calicheamicin DMH AcBut. Metabolites M5, M6, M7, M8, M9a and M9b were also detected as cytosol metabolites of NAc-gamma

calicheamicin DMH (see Section 3.5.2.3.1.3.2.2). M6 was found to be NAc-epsilon calicheamicin. M5 (NAc-epsilon calicheamicin + 2H) and M7 (isomer of NAc-epsilon calicheamicin) were derivatives of NAc-epsilon calicheamicin. The

data on M8, M9a, and M9b were inconclusive.

The molecular weight of M8 was 1002 Da with an intact acetylated ethylamino sugar; however, the structure was not identified. Molecular weights of M9a and M9b were 417 Da and 419 Da, respectively. M11a and M11b (NAc-epsilon calicheamicin + O) and M15a and M15b (NAc-epsilon calicheamicin + 2H + O) were formed after incubation with NAc-gamma calicheamicin DMH AcBut.

- Appropriate metabolism information including activity of the metabolites has not been submitted in order for the Agency to assess the necessary and appropriate drug interaction studies and impact on safety. On December 17th, 1999 (post 45-day filing meeting) we requested additional information regarding isozyme involvement in the metabolism cascade and further information on which metabolites are believed to be active.
- In summary, 11 metabolites of NAc-gamma calicheamicin DMH were found after incubation in human liver microsomes and cytosol. The biotransformation pathways identified in microsomes were oxygenation 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, suggesting that the metabolism of the calicheamicin derivatives may not be cell specific. The detection of NAc-epsilon calicheamicin and its derivatives in cells may indicate that the reactive diradical species of NAc-epsilon calicheamicin may be formed via a glutathione-dependent reduction of the disulfide bond of NAc-gamma calicheamicin DMH within cells.

APPEARS THIS WAY
ON ORIGINAL

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW
PHARMACOMETRICS REVIEW

NDA 21,174

Submission Date: October 29, 1999
 December 13, 1999
 March 27, 2000

Drug Name:	Gemtuzumab Zogamicin
Formulation:	IV injection, 5 mg in a vial
Applicant:	Wyeth-Ayerst Laboratories
Consult:	Report: "Population Pharmacokinetics of HP67.6 Following Administration of Gemtuzumab Zogamicin in Patients with Acute Myeloid Leukemia"
Pharmacometrics	
Specialist:	Elena V. Mishina, Ph.D.

Preamble/Background:

Gemtuzumab zogamicin for injection is the first of a new class of antineoplastics characterized as "antibody-targeted chemotherapy". Gemtuzumab zogamicin binds specifically to the CD33 antigen. This antigen is expressed on the surface of leukemic blasts in more than 80% of patients with acute myeloid leukemia (AML). CD33 is also expressed on normal and leukemic myeloid colony-forming cells, including leukemic clonogenic precursors; however, it is not expressed on pluripotent hematopoietic stem cells or on nonhematopoietic cells. This property of the CD33 antigen makes it possible to use an anti-CD33 antibody to target the delivery of a cytotoxic agent to leukemia cells.

The pharmacokinetics of gemtuzumab zogamicin has been characterized by the measurement of the anti CD33 antibody (hP67.6) in the plasma of patients with CD33 positive AML.

The applicant has conducted a number of pharmacokinetic studies. Population pharmacokinetics data analysis was performed combining the data from four of them:

0903A1-101-US, early Phase I;

0903B1-201-US, Phase II;

0903B1-202-EU, Phase II;

0903B1-203-US/EU, Phase II.

The purpose of this analysis was to determine an appropriate compartmental model, error structures and to investigate the possible influence of patient demography on the pharmacokinetics of anti CD33 antibody. The possible covariates included patient age, body surface area, gender, and ethnic origin.

Question:

Is the population pharmacokinetics data analysis of CMA676 acceptable?

Methods:

Population pharmacokinetic analysis included all patients' data that had any measurable concentration of hP67.6. The applicant reported that a total of 142 patients receiving 275 doses of gemtuzumab zogamicin were included in the analysis. A total of 2468 non-zero hP67.6 concentrations were used to develop a population pharmacokinetic model. However, data file submitted to the Agency for NONMEM analysis contained data from 180 patients.

Modeling:

The applicant evaluated both a one-compartmental and a two-compartmental models, and various residual error structures, and different statistical structure of parameters for inter-individual variability. A significant change was observed between the first and second dose period. Various models that incorporated the dose period as a fixed parameter were explored. The applicant claimed that the possible covariates have been tested.

The applicant explained the different steps of model building. Final model CMA016 to describe the pharmacokinetics of hP67.6 was two-compartmental model with inter-individual error terms on clearance (CL) and volume of distribution (V1) and estimation of the additive and proportional residual errors as population parameters. The applicant referred to the graphical evaluation of criteria of goodness of fit (plots of individual predicted and observed plasma concentrations, weighted residuals vs time, weighted residuals vs predicted concentrations, population predicted vs observed concentrations).

Six patients in the CMA analysis had distinctly different pharmacokinetic parameters. The applicant could not justify that these patients were the outliers, and could not prove that the inclusion or exclusion of their data had influence on the estimated parameters. Nevertheless, the individual parameters estimated from these patients were omitted from the diagnostics plots.

Results:

Addition of dose period as a fixed parameter was justified by the statistically significant decrease in the objective function (OBJ) by 12 units (models CMA004 and CMA009). On average, the decrease in clearance after the second dose was estimated by factor 0.777, which is about 20% of the first dose and may be considered clinically irrelevant. However, in the study report 0903B1-203-US/EU, volume 67, the comparison of parameters estimated by non-compartmental method (Table 1) shows that exposure to the drug measured by the area under the curve increased 2.5-fold after the second dose (n=14) in comparison to the first dose (n=20). Similar results were found for the study 0903B1-201-US, where the mean CL value was 2 fold lower for the second dose in comparison with the first dose. The applicant explained these discrepancies based on high variability of the estimated parameters. Considering the high clearance variability (CV ~ 100%) for the population model, these differences in clearance between the first and second doses may not be clinically significant.

Table 1. Pharmacokinetic Results of the Study 0903B1-203-US/EU.

SYNOPSIS

COMPANY NAME: Wyeth		INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER		<i>(For National Authority Use Only)</i>		
NAME OF FINISHED PRODUCT: <Trademark name> To be determined		VOLUME:				
NAME OF ACTIVE INGREDIENT: Gemtuzumab zogamicin [CL-555201]		PAGE:				
Dose Period	C _{max} mg/L	t _{1/2} h	λ _z * h ⁻¹	AUC* mg•h/L	CL L/h	V _{ss} L
1 (n=20)	2.45 ± 1.12	63.0 ± 39.2	0.0153 ± 0.0101	122 ± 137	0.326 ± 0.367	17.7 ± 13.1
2 (n=14)	3.55 ± 2.12	103.4 ± 67.3	0.0090 ± 0.0045	301 ± 217	0.119 ± 0.138	10.2 ± 8.3
* Statistically significant difference between dose period 1 and 2 (p < 0.05)						

However, the difference in the exposure as measured by AUC was not addressed in the proposed model.

The population pharmacokinetics study report submitted in the NDA used the data for patients; however submitted data file included the data from 180 patients. Therefore, the value of the objective function obtained by the reviewer was much higher (41637) than the one reported by the applicant (34398). Nevertheless, parameter estimation was very similar with the reported by the applicant.

The reviewer verified the graphical model diagnostics based on the submitted by the applicant model and data files.

Population Predictions

The applicant presented Figure 1 to show population predicted and observed plasma concentrations vs time. Based on Figure 1, it is difficult to assess visually how well the population model predicts the observed individual patients' data.

FIGURE 1. OBSERVED AND PREDICTED PLASMA CONCENTRATIONS OF hP67.6 VERSUS TIME

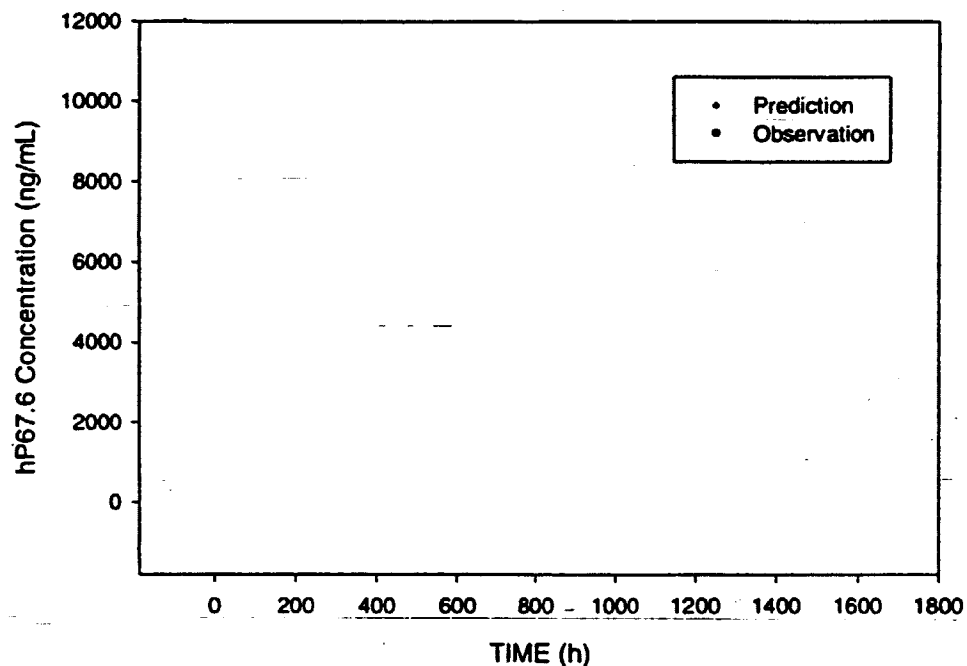
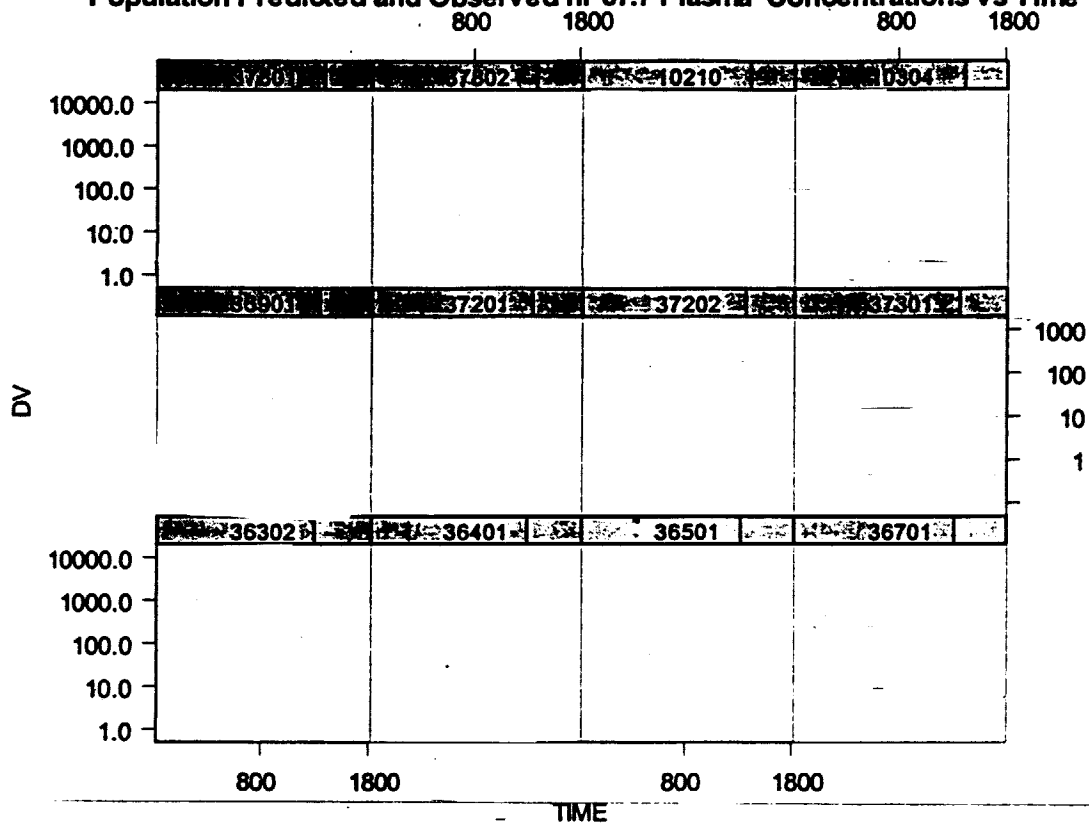


Figure 2 shows the randomly chosen plots of population predicted and observed plasma hP67.6 concentration vs time for 24 out of 180 individuals. In this Figure and later in the review DV means "Plasma hP67.6 concentration". Figure 2 indicates that the drug plasma concentrations were underestimated-by the population model at high concentrations and overestimated at low plasma concentrations.

The plot of population predicted vs observed plasma concentrations gives the most important information for the assessment of goodness of fit (Figure 3). The skewness of this plot indicates that the proposed model is biased and does not provide the optimal population estimates. Apparently, the model predicts higher than observed plasma concentrations at low concentrations. It predicts lower than observed plasma concentrations at high concentrations. Although the applicant commented on the influence of six patients whose parameters were very different from the rest of the population, the explanation on the skewness of this plot were not available for review.

Figure 2.

Population Predicted and Observed hP67.7 Plasma Concentrations vs Time



DV = Plasma hP67.6 concentration

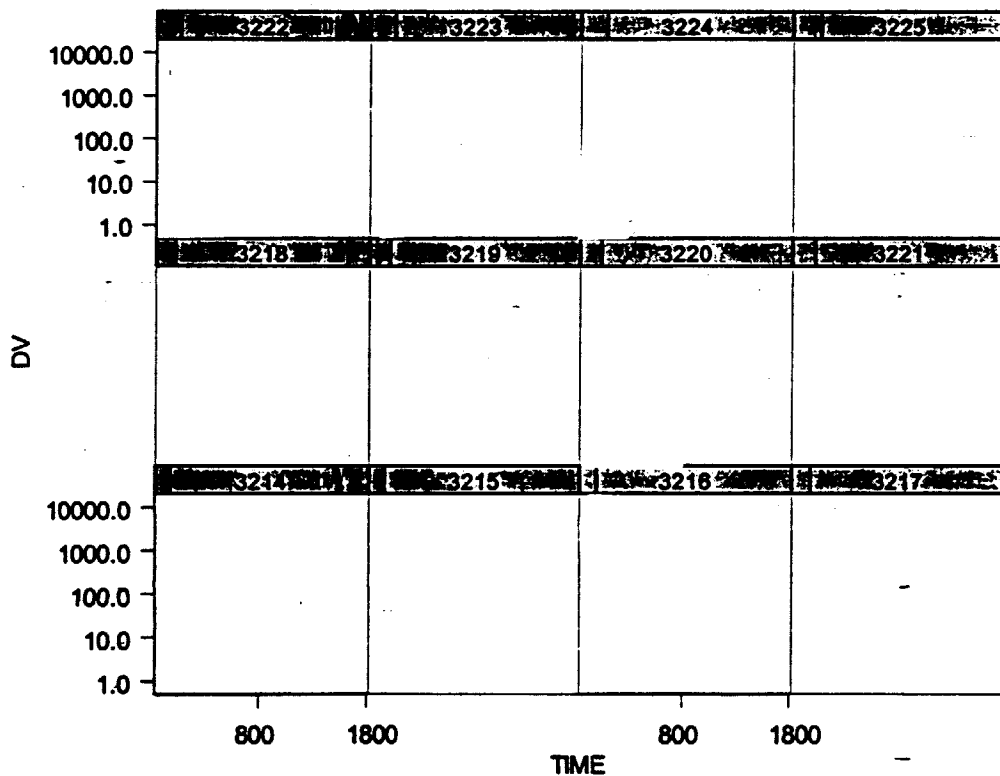
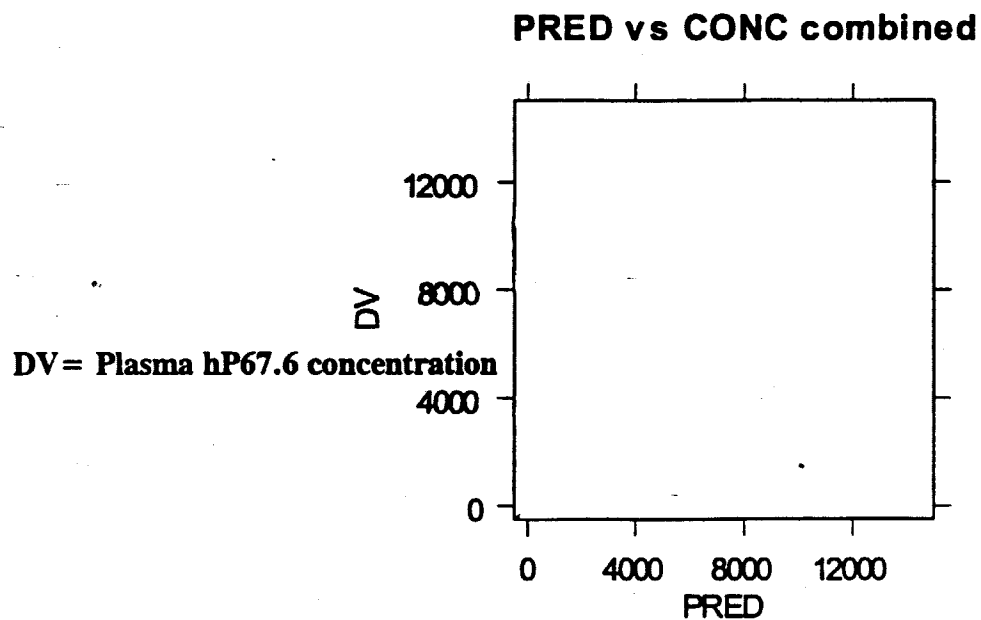
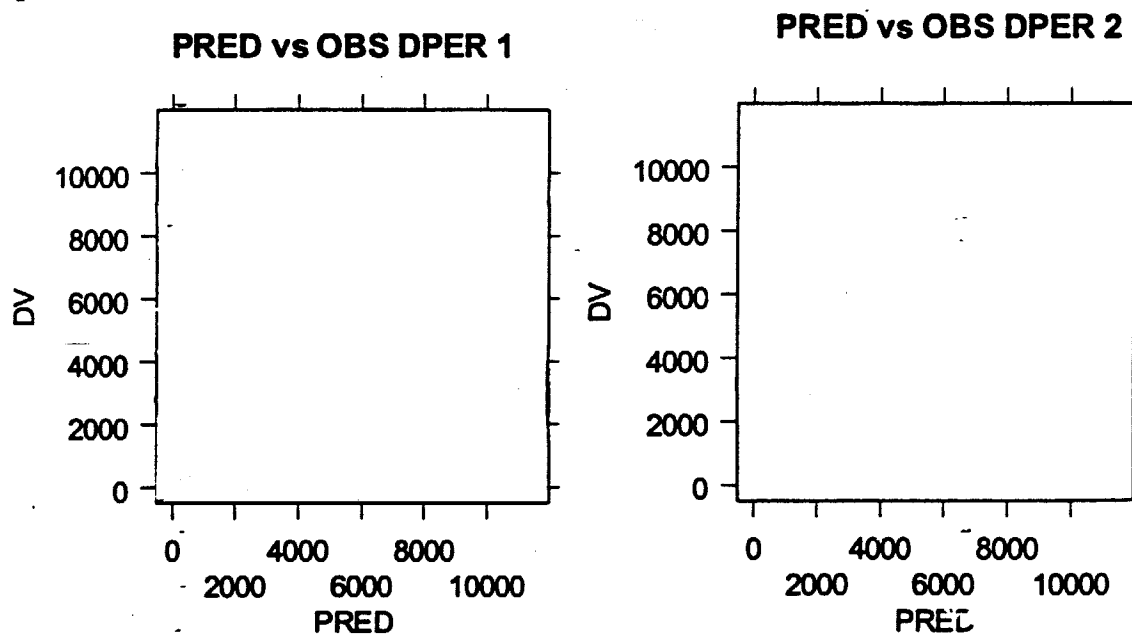


Figure 3. Population Predicted vs Observed Plasma Concentrations



The skewness of the population prediction for plasma concentrations was the same for both dose periods, see Figure 4.

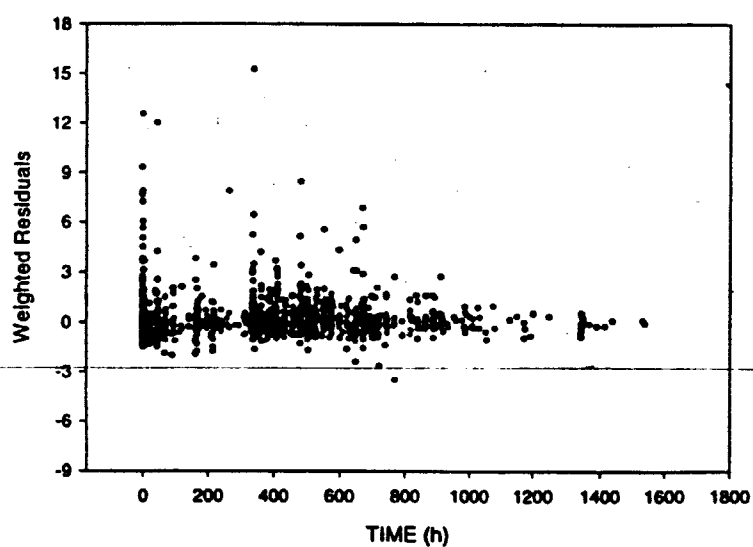
Figure 4. Population predicted vs observed plasma concentrations for dose periods 1 and 2



Another model diagnostics tool is plot of residuals vs time. The applicant chose to show the plot for weighted residuals vs time (Figure 5). In this case, the values of residuals are multiplied by the weight (weight = $1/y$). This plot artificially diminishes the values of residuals. Nevertheless, this plot also indicates the bias estimates obtained by the population model.

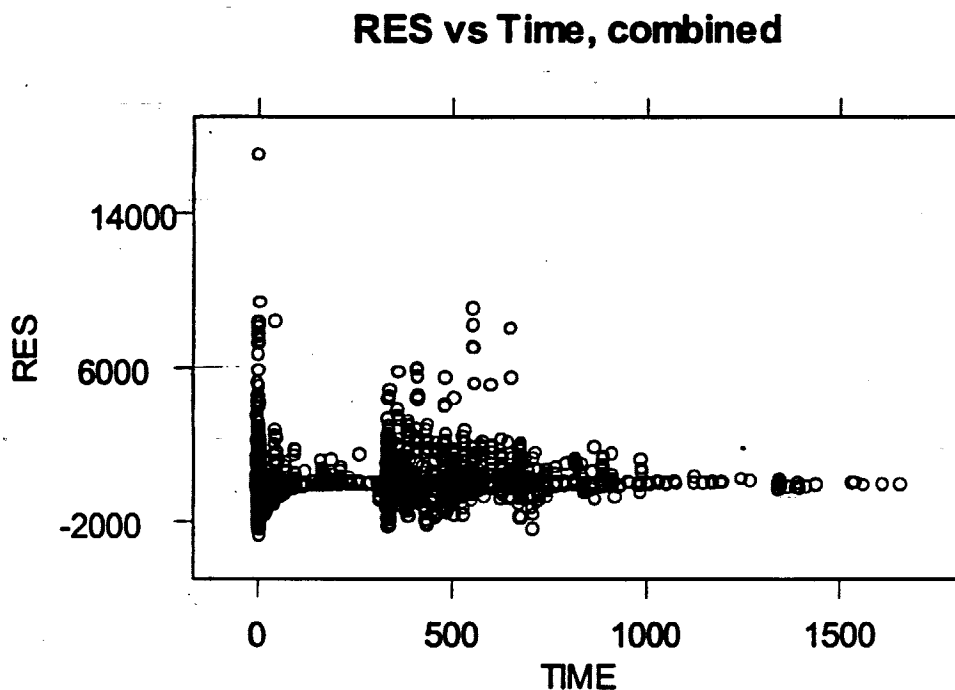
Figure 5.

FIGURE 4. WEIGHTED RESIDUALS VERUS TIME



The plot of residuals vs time or vs plasma concentration (Figure 6) emphasizes the bias estimates obtained by the model.

Figure 6. Residuals vs Time.



Individual Patients' Predictions

The applicant presented the individual patients' predicted vs observed plasma concentrations in the same manner as in Figure 1, and it is difficult to understand how well the model predict the individual patients' data.

Figure 7 (FDA assessment) gives a randomly chosen example of individual predicted and observed plasma concentration vs time for 24 patients. The model reasonably predicts the individual patients' data; however, the predictions for through plasma concentrations were overestimated for almost all patients. This is concurrent with the previously found biases in the population model although the individual predictions are much better than the population predictions (Figure 8).

Figure 7. Individual Observed and Predicted CMA676 Concentrations vs Time

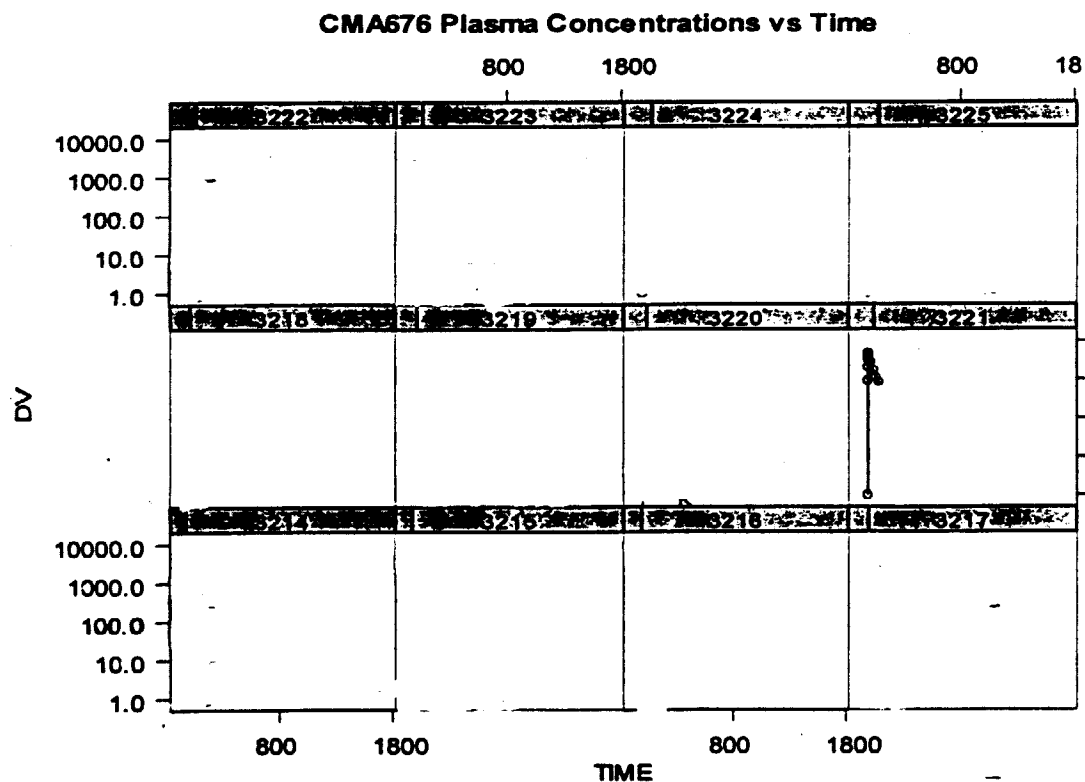
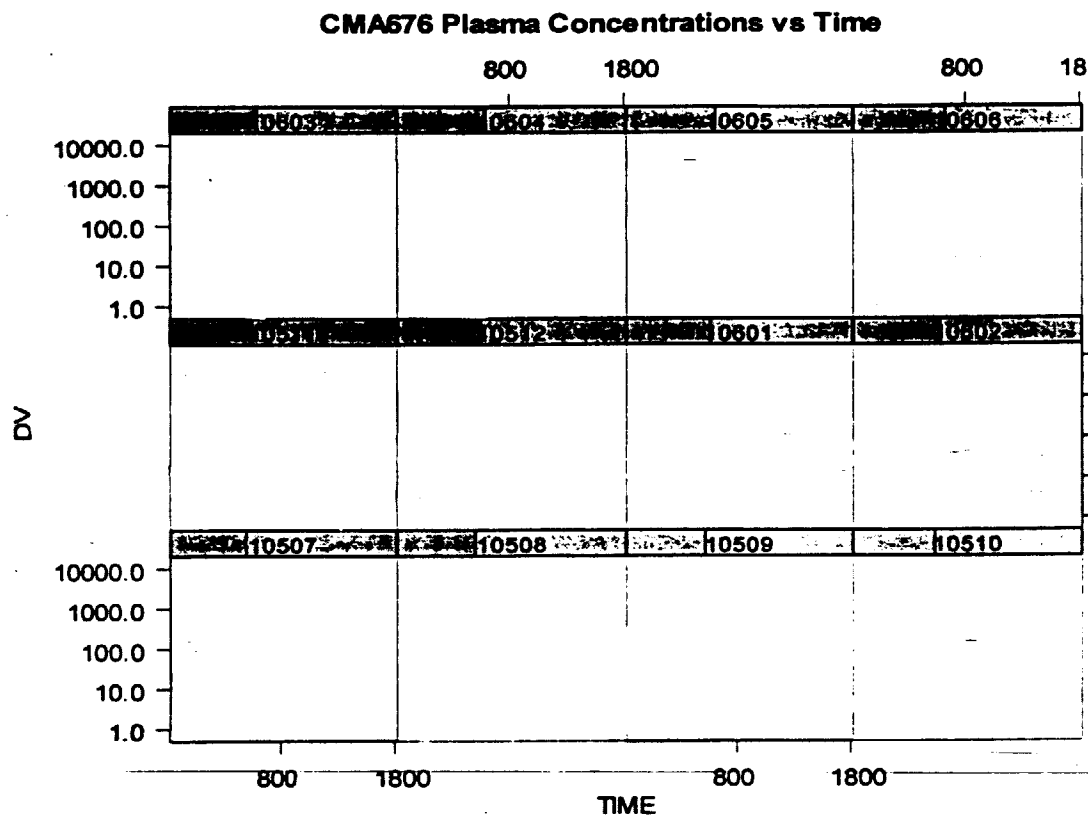
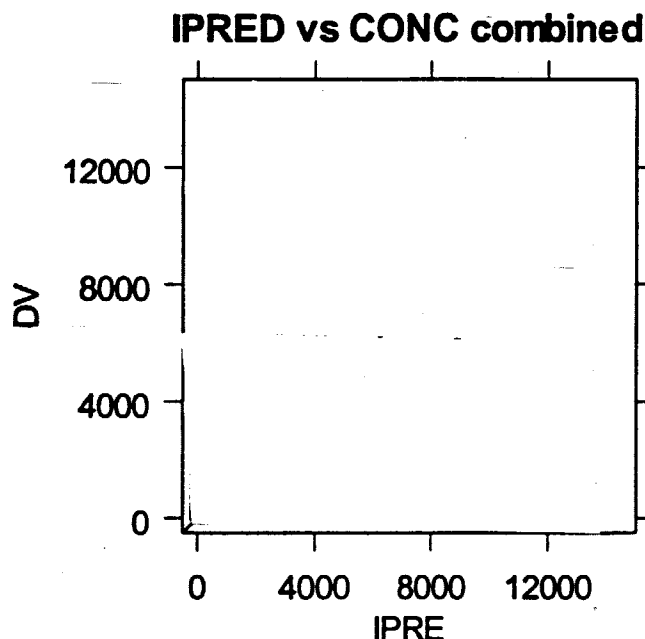


Figure 8. Individual Predicted vs Observed Plasma Concentrations



DV = Plasma hP67.6 concentration

Additionally, the applicant submitted the plots of weighed residuals for the individual predictions and we mentioned previously that this information is not very valuable in the assessment of the goodness of fit of the population model.

Covariates Testing

Normally, the assessment of the covariates is performed with the use of NONMEM, by incorporation of the studied covariates into the equation for the fixed effect parameters. The applicant performed an evaluation of the covariates based on the visual comparison of the plots of examined parameters (clearance and volume) vs the demographic variables.

The Oncologic Drug Advisory Committee based on improved safety and acceptable efficacy, recommended approval of gemtuzumab zogarnicin for the treatment of acute myeloid leukemia in a subgroup of patients 60 years of age and older. Therefore, it is important to statistically evaluate the influence of age as a covariate using NONMEM.

Additionally, the important covariate to assess in this NDA will be the hepatic function since the drug is extensively metabolizes and has a substantial hepatic toxicity.

In conclusion, based on the review findings, the population pharmacokinetics data analysis of CMA676 is not acceptable from the point of view of the Office of Clinical Pharmacology and Biopharmaceutics.

Comments

5. The applicant explained the different steps of population pharmacokinetic model building and choosing the optimal model to fit the data based on model diagnostics. Final model CMA016 to describe the pharmacokinetics of hP67.6 was two-compartmental model with inter-individual error terms on clearance and volume of distribution and estimation of the additive and proportional residual errors as population parameters. The graphic diagnostics of the final model verified by the Agency showed that it is not optimal. It predicts higher than observed plasma concentrations at low concentrations, and lower than observed plasma concentrations at high concentrations. Although the applicant commented that six patients had very different from the rest of the population parameter estimations, this alone cannot explain the poor fit of the model. The applicant should attempt to optimize the model and submit the results to the Agency for review.
6. The decrease in clearance after the second dose was estimated about 20% of the clearance after the first dose and may be considered clinically irrelevant. However, in the study reports 0903B1-201 and 0903B1-203, the differences in clearance after the first and second dose were above 2 fold, which accounts for approximately half of all studied patients. Patients with this difference in the exposure may be the candidates for dose adjustment. Therefore, the differences in the observed clearance between the first and second dose in the referred studies are not in agreement with the 20% difference in the population clearance values predicted by the model. The Agency recommends that the applicant re-evaluate the influence of the second dose on the clearance by the population modeling.
7. The applicant tested the influence of the demographic covariates on the pharmacokinetic parameters (clearance and volume) based on the visual comparison of the plots of examined parameters. Since gemtuzumab zogamicin is recommended in the narrow patients' population of 60 years of age and older, the applicant is recommended to statistically evaluate the influence of age as a covariate. The applicant should incorporate age as a covariate into the equation for the fixed effect parameters using NONMEM.
8. The applicant is recommended to statistically evaluate the hepatic function as a covariate since gemtuzumab zogamicin is extensively metabolized, excreted by liver and bile, and has a substantial hepatic toxicity.

Recommendation:

The Office of Clinical Pharmacology and Biopharmaceutics reviewed the Report: "Population Pharmacokinetics of hP67.6 Following Administration of Gemtuzumab Zogamicin in Patients with Acute Myeloid Leukemia". The population analysis is not acceptable based on: poor model predictions, poor evaluation of the difference in clearance between the first and second doses, and the absence of covariate analysis.

The comments 1-4 should be conveyed to the applicant.

/S/

4/24/00 Date

Elena Mishina, Ph. D.
Pharmacometrics Specialist

/S/

4/24/00

Atiqur Rahman, Ph. D.
Oncology Team Leader

cc list: NDA 21-174, HFD-150,

Appendix A

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information

Proposed Labeling

APR 20 2000

Clinical Pharmacology and Biopharmaceutics Protocol Review

FAX Submission Date: April 7, 2000

NDA 21-171

Drug Name: GO (gemtuzumab ozogamicin, CMA-676, CL-555201)

Formulation: Intravenous, 5 mg/vial, 0.25 mg/mL conc.

Applicant: Wyeth-Ayerst Research
Philadelphia, PA

Primary Reviewer: Lydia Velazquez Kieffer, Pharm.D.

Team Leader: Atiqur Rahman, Ph.D.

Type of Submission: New Protocol

Background: The review evaluates protocol 0903B1-302-US entitled: "A randomized controlled trial of gemtuzumab ozogamicin (GO) given in combination with cytarabine and daunorubicin versus cytarabine and daunorubicin for remission induction and post-remission therapy in younger de novo patients with acute myeloid leukemia (AML)." from the Clinical Pharmacology and Biopharmaceutics perspective. GO is an antibody-targeted chemotherapy agent. The compound consists of a human engineered anti-CD33 antibody linked to calicheamicin, a cytotoxic antibiotic. The CD-33 antigen is expressed on the surface of leukemic blasts in a high percentage of patients with acute myeloid leukemia (AML). GO binds to CD33 on the surface of leukemic blasts and is then internalized. Once inside the cell, hydrolysis of the linker takes place which allows calicheamicin to be released and exert its antineoplastic effects. GO is distributed to leukemia cells that are CD33 positive and hematopoietic cells.

The applicant's proposed protocol objectives are: 1) to assess and compare the efficacy of each regimen in terms of the number of patients attaining a complete remission (CR) and complete remission without full platelet recovery (CRp), 2) to assess and compare the duration of remission, 3) to assess and compare survival. Secondary objectives include: 1) to investigate the relationship between minimal residual disease and relapse of AML, 2) to assess and compare the safety of each leukemia induction regimen.

Comments:

1. The study design states that the applicant intends to examine a different patient population (older patients with de novo AML) from what is stated in the title and inclusion criteria (younger patients with de novo AML). Please clarify.
2. Please provide rationale for maintaining the GO dose at 9 mg/m² in this combination regimen.
3. Please provide the pharmacokinetic and pharmacodynamic plan for study 0903B1-302-US.

4. The applicant is strongly recommended to submit a pharmacokinetic and pharmacodynamic plan for future Phase I studies to explore pharmacokinetic interactions between GO and other cytotoxic agents intended as combination therapy.

Recommendation:

The proposed protocol is deficient from the Clinical Pharmacology and Biopharmaceutics perspective. Please forward the above comments to the sponsor.

1
151
Lydia Velazquez Kieffer, Pharm.D.

Reviewer

Division of Pharmaceutical Evaluation I

Date 4-20-00

151
Atiqur Rahman, Ph.D.

Team Leader

Division of Pharmaceutical Evaluation I

4/20/00

cc: Orig IND

NDA 21-174

HFD-150/ Division File

HFD-150/ SBradley, JBeitz, PBross, XChen, EDuffy, RSandip, PAndrews

HFD-860/ MMehta, ARahman, LVelazquezKieffer