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APPLICATION NUMBER:

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NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY BLA REVIEW AND EVALUATION

Application number:	761060
Supporting document/s:	1
Applicant's letter date:	November 2, 2016
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Product:	MYLOTARG® (gemtuzumab ozogamicin for Injection)
Indication:	Combination Therapy with Daunorubicin and Cytarabine for Previously Untreated de novo and Relapsed AML
Applicant:	Pfizer
Review Division:	Division of Hematology Oncology Toxicology (DHOT) for Division of Hematology Products (DHP)
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1 Executive Summary

1.1 Introduction

Mylotarg (gemtuzumab ozogamicin) is an antibody drug conjugated (ADC) product composed of a recombinant human-mouse IgG4 kappa antibody gemtuzumab, specific for human CD33 antigen, covalently linked to the cytotoxic agent N-acetyl gamma calicheamicin. Mylotarg was granted approval in 2000 under accelerated approval regulations that requires a clinical trial to verify clinical benefit. The accelerated approval was withdrawn in 2010 based on lack of efficacy and safety concerns in the confirmatory trial.

Pfizer submitted the current Biological License Application (BLA) for Mylotarg indicated for the treatment of:

1. Patients with untreated de novo acute myeloid leukemia (AML) in combination with daunorubicin (DNR) and cytarabine (AraC) and
2. Patients with AML in first relapse who are 60 years of age or older and who are not considered candidates for other cytotoxic chemotherapy

The recommended dose of GO is 3 mg/m² up to a maximum dose of 5 mg, infused over a 2-hour period on Days 1, 4, and 7 in combination with DNR and AraC.

The nonclinical development program of gemtuzumab ozogamicin (GO) included all study reports previously submitted to the NDA that was granted approval in 2000. The nonclinical toxicology profile of GO indicates that it is hepatotoxic, nephrotoxic, and myelotoxic in rats and monkeys at doses of ≥7.2 mg/m^2. GO is clastogenic and N-Ac-γ-calicheamicin DMH was mutagenic and clastogenic in in vitro tests. Additionally, GO is embryotoxic and reprotoxic at approximately similar human clinical exposure after repeat doses of 3 mg/m^2. From the perspective of nonclinical pharmacology and toxicology, there are no outstanding issues that prevent the approval of this BLA.

1.2 Brief Discussion of Nonclinical Findings

The nonclinical data submitted to the BLA provided evidence that CMA-676 (GO) and the unconjugated hP67.6 antibody have binding affinities (KD) for a soluble form of CD33 in the low nanomolar range (0.07 to 0.08 nM) and the affinity was not affected by the conjugation of calicheamicin to hP67.6 antibody. The unconjugated hP67.6 antibody did not exhibit specific staining to any tissues in rats and monkeys models used in toxicity studies. CMA-676 was very potent and demonstrated high selectivity for CD33+ target cells relative to CD33- control cells. CMA-676 was 1000-fold more cytotoxic to HL-60 cells than a comparable conjugate made with a non-targeting control antibody, and the unconjugated hP67.6 antibody showed no cytotoxicity in this assay. CMA-676 also showed an in vivo dose-response effect with >80% inhibition of tumor growth at doses between 0.8 and 2.4 mg/m^2 NAc-gamma calicheamicin DMH equivalents. In safety pharmacology studies, GO was associated with reductions in mean arterial blood pressure, increases in heart rate and increases in P- and T-wave amplitude at ≥13 mg/m^2.

Pharmacokinetic studies in rats and monkeys with the drug substance showed that very little dissociation of calicheamicin occurred in vivo. The half-life was long (3-7 days) characteristic for an immunoglobulin. The half-life in monkeys was much greater than in rodents.

Repeat-dose studies included six cycle intravenous toxicity studies in rats and monkeys and a six cycle comparative study in monkeys for the old and new antibody cell lines. Rats were administered 6 weekly doses at 0 (PBS control), 7.2 (hP67.6 antibody control), or CL 555,201 (GO) at doses of 0.6, 2.4, or 7.2 mg/m^2/week and observed for an additional 4 weeks. GO-related decreases in red blood cell mass and microscopic findings mostly observed at ≥2.4 mg/m^2/week in the kidney, liver, spleen, bone marrow, testes/epididymides, and male mammary gland which were still present at the end of the 4-week recovery period. Monkeys were administered 6 weekly IV doses at 0 (PBS control), 22 (hP67.6 antibody control), or CL 555,201 at doses of 2.4, 7.2, or 22 mg/m^2/week (5, 15 or 45 mcg/kg/week calicheamicin equivalents) and observed for an additional 4 weeks. GO-related decreases in red blood cell mass, WBC, polymorphonuclear cells, and lymphocytes alone with higher AST, total protein, globulin, and sodium, and lower albumin and albumin/globulin ratio (A/G) mostly observed at ≥2.4 mg/m^2/week. Microscopic findings in monkeys were observed mostly in ≥7.2 mg/m^2/week in the kidney, liver, thymus, spleen, lymphatic tissues, and bone marrow. In the comparative study, similar toxicological and systemic exposure profile was observed between the old and new antibody cell lines. Marked eosinophilia occurred at all dose levels and was associated with hypersensitivity reactions in few monkeys dosed with the old cell line. Target organ of toxicity for OG included the bone marrow, kidneys, liver, skeletal muscle, spleen, thymus and testes with decreases in absolute and adjusted organ weights and microscopic correlates that included degeneration of seminiferous tubules and lymphoid depletion in testes and thymus.

Embryofetal Developmental studies conducted were ICH stage C-D studies with CMA-676 in time-mated female CD VAF (virus antibody free) rats. Based on the unequivocally positive results obtained from a pilot study, the Agency previously agreed with the Applicant that one species would be sufficient to support an NDA application for CMA-676 in a leukemia indication. Daily maternal treatment of rats during the period of organogenesis from GD 6 to GD 17 with CMA-676 at 0, 0.010, 0.025, or 0.060 mg/kg/day (0, 0.06, 0.15, or 0.36 mg/m^2) produced increased embryofetal mortality, decreased numbers of live fetuses per litter, and low fetal incidences of gross external, visceral and skeletal anomalies. Effects on fetal weight, ossification, and wavy ribs became apparent at 0.025 mg/kg/day. Since peri- and postnatal studies were not conducted, no information is available on the effect of CMA-676 on parturition, lactation, functional development, locomotion or learning ability.

Fertility studies conducted were ICH stage A-B modified studies with male and female CD-IGS rats dosed only during the pre-mating period. Male and female rats received GO at doses of 0, 0.02, 0.06, or 0.18 mg/kg/day (0, 0.12, 0.36, or 1.08 mg/m^2/day). Males were dosed daily for 28 days and females daily for 14 days before mating with untreated partners. In females, increased embryofetal lethality occurred at ≥0.36 mg/m^2

in the presence of maternal toxicity that included decreases in gestational body weight and food consumption. In males, lower spermatogonia and spermatocytes, decreases in testicular spermatids and epididymal sperm, vacuolation of the nucleus in spermatids, and/or appearance of giant cells occurred at ≥0.12 mg/m^2/day. Additional findings included effects on the testes (≥0.12 mg/m^2/day) and epididymides (≥0.36 mg/m2/day); both organs were macroscopically small and decreased in weight as well as decreased fertility.

1.3 Recommendations

1.3.1 Approvability

There are no outstanding issues from a pharmacology/toxicology perspective that would prevent that prevent the approval of this BLA.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

The nonclinical sections of the label were discussed previously with the review team and recommendations to meet PLLR current regulations sent to the Applicant.

2 Drug Information

2.1 Drug

CAS Registry Number
220578-59-6

Generic Name
Gemtuzumab ozogamicin (GO)

Trade Name
Mylotarg®

Code Name
CMA-676, PF-05208747, CL-555,201, hP67

Chemical Name
Conjugate of humanized CD33-directed monoclonal IgG4 antibody covalently linked to the cytotoxic agent N-acetyl gamma calicheamicin

Molecular Mass
152-153 KDa

Gemtuzumab ozogamicin drug substance has heterogeneity in composition of glycans and number of calicheamicin derivative conjugated per gemtuzumab molecule. As a result, definitive molecular mass is not applicable. For the predominant N-glycoform of

gemtuzumab ozogamicin with 2 and 3 calicheamicin derivative moieties attached, the theoretical molecular masses are 151,520 Da and 153,185 Da, respectively.

Structure or Biochemical Description

Gemtuzumab

Recombinant, humanized monoclonal antibody (IgG4 with kappa light chains) that binds to the CD33 antigen expressed on the surface of leukemic cells.

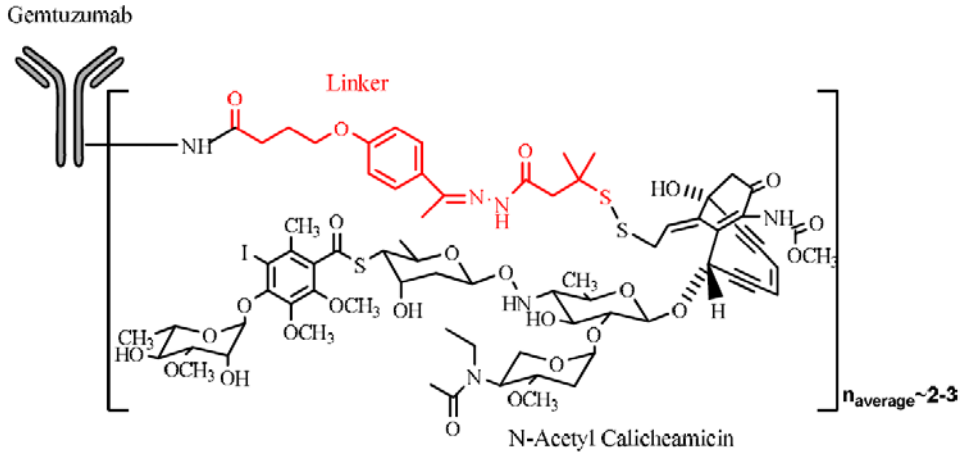
Figure 1 Structure of Gemtuzumab Antibody

(Excerpted from Submission)

Gemtuzumab Ozogamicin

Figure 2 Structure of Mylotarg

(Excerpted from Submission)



The ADC consists of 3 components: 1) the recombinant human-mouse IgG4 kappa antibody gemtuzumab, specific for human CD33 antigen, 2) N-acetyl-gamma-calicheamicin that causes DNA double strand-breaks, and 3) an acid-cleavable linker composed of the condensation product of AcBut and 3-methyl-3-mercaptobutane hydrazide (known as dimethylhydrazide) that covalently attaches N-acetyl-gamma-calicheamicin to gemtuzumab

Pharmacologic Class
Antibody Drug Conjugated (ADC)

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 046635, NDA 021174

2.3 Drug Formulation

The drug product is supplied in a 20 mL amber vial designed to deliver 5 mg of gemtuzumab ozogamicin in 5 mL of solution sealed with a rubber stopper and aluminum seal. Inactive excipients are sodium chloride, sucrose, dextran 40, and sodium phosphate salts. Following reconstitution with 5 mL of sterile water for injection, the solution is further diluted with sterile saline and administered to patients by intravenous infusion. The drug product contains no preservatives and is for single use only.

Table 1 Composition of Gemtuzumab Ozogamicin Drug Product

(Excerpted from Submission)

Name of Ingredients	Reference to Standard	Unit Formula (mg/vial)
Gemtuzumab Ozogamicin	Internal Specification	(b) (4)
Sucrose	NF, Ph.Eur., JP	
Dextran 40	USP, Ph.Eur., JP	
Sodium Chloride	USP, Ph.Eur., JP	
Monobasic Sodium Phosphate, Monohydrate	USP	
Dibasic Sodium Phosphate, Anhydrous	USP, Ph.Eur., JPE	

2.4 Comments on Novel Excipients

None

2.5 Comments on Impurities/Degradants of Concern

None

2.6 Proposed Clinical Population and Dosing Regimen

Gemtuzumab ozogamicin (Mylotarg) is indicated for the treatment of:

3. Patients with untreated de novo acute myeloid leukemia in combination with daunorubicin and cytarabine and
4. Patients with AML in first relapse who are 60 years of age or older and who are not considered candidates for other cytotoxic chemotherapy

The recommended dosing regimen of GO in combination with DNR and AraC for treatment of patients with previously untreated de novo AML is as follows:

- Induction: The recommended dose of GO is 3 mg/m² up to a maximum dose of 5 mg, infused over a 2-hour period on Days 1, 4, and 7 in combination with DNR 60 mg/m²/day infused over 30 minutes on Days 1, 2, and 3 and AraC 200 mg/m²/day by continuous infusion on Days 1 to 7.
- Consolidation: For patients achieving CR, defined as fewer than 5% blasts in a normocellular marrow and an absolute neutrophil count (ANC) of more than 1.0×10^9 cells/L with a platelet count of 100×10^9 cells/L or more in the peripheral blood,

2.7 Regulatory Background

Mylotarg was initially approved on May 17, 2000 under accelerated approval regulations (21 CFR 314 subpart H) for the treatment of patients with CD33 positive acute myeloid leukemia first relapse who are 60 years of age or older and who are not considered candidates for cytotoxic chemotherapy. Wyeth Pharmaceuticals Inc. (Wyeth), the applicant holder for NDA 21174, was later acquired by Pfizer, Inc. A clinical trial to fulfill the subpart H requirement to verify clinical benefit was terminated early due to lack of efficacy and the observation of more induction phase deaths on the Mylotarg plus chemotherapy study arm compared to the chemotherapy alone arm. As a result, the accelerated approval granted in 2000 was withdrawn on June 18, 2010. The NDA 21174 is still active though Mylotarg was not marketed in the USA.

3 Studies Submitted

3.1 Studies Reviewed

Primary Pharmacology

RPT-56053: Use of (b) (4) surface plasmon resonance to determine the binding affinity of CMA-676 and hP67.6 to CD33

MIRACL-26808: Cross reactivity of humanized monoclonal antibody hP67.6 with tissues of Cynomolgus monkeys and Sprague-Dawley rats

Toxicology

GRT-27677: CMA-676: Six cycle intravenous comparative toxicity study in male monkeys

40230: CMA-676: Intravenous Female Fertility Study in Rats

40369: CMA-676: Intravenous Male Fertility Study in Rats

3.2 Studies Not Reviewed

See list in 10 Appendix/Attachments

3.3 Previous Reviews Referenced

All study reports indicated as previously reviewed are reference to Dr. Paul A. Andres' review from 1994 to 1996 for NDA 021174.

4 Pharmacology

4.1 Primary Pharmacology

Study No. RPT-56053: Use of (b) (4) surface plasmon resonance to determine the binding affinity of CMA-676 and hP67.6 to CD33

The binding of CMA-676 and hP67.6 antibody to CD33 was evaluated using (b) (4) SPR (surface plasmon resonance). Affinity constants of several CMA-676 batches were compared to those determined for the unconjugated hP67.6 antibody. The effect of storage of CMA-676 at 2- 8°C and incubation at (b) (4) C was also evaluated.

Table 2 Summary of CMA-676 and hP67.6 Binding Constants to CD33

(Excerpted from Submission)

Sample	KD (nM)	Kd (1/s)	Ka (1/Ms)
P67.6, Batch No. K9186	0.077	1.4×10^{-5}	1.8×10^{5}
P67.6, Batch No. K9212	0.069	1.3×10^{-5}	1.9×10^{5}
Gemtuzumab Ozogamicin			
BA No. RS 974-1[a]	0.082	1.5×10^{-5}	1.8×10^{5}
BA No. RS 974-1[b]	0.082	1.5×10^{-5}	1.8×10^{5}
BA No. 136A1[c]	0.086	1.6×10^{-5}	1.9×10^{5}
BA No. 111A1[d]	0.076	1.5×10^{-5}	1.9×10^{5}
BA No. 103A[e]	0.082	1.5×10^{-5}	1.9×10^{5}
BA No. 030YTEC[f]	0.079	1.5×10^{-5}	1.9×10^{5}
BA No. 101A042Y[g]	0.075	1.4×10^{-5}	1.9×10^{5}

Source: RPT-56053

[a] Freshly prepared; [b] Stored at 2 to 8°C for 0.5 months; [c] Stored at 2 to 8°C for 8 months; [d] Stored at 2 to 8°C for 45 months; [e] Commercial Lot, Stored at 2 to 8°C for 52 months; [f] Stability batch; stored at 2 to 8°C for 64 months; [g] 30°C/ 60% RH for 3 months then 2 to 8°C for 48 months

Ka = Association constant; Kd = Dissociation constant; KD - Equilibrium dissociation constant; M = Molar; Ms = Millisecond; s = Second

hP67.6 exhibited KD for a soluble form of CD33 in the low nanomolar range (0.07 to 0.08 nM) and the affinity was not affected by the conjugation of calicheamicin to hP67.6 antibody, nor was it compromised by long incubations of the conjugate at 2-8°C for up to (b) (4) months. Estimates of the affinity constants for all samples tested were within a narrow range, from 0.075 to 0.086 nM. Association and dissociation constants, Ka and Kd, for all samples were between 1.8 and 1.9 x 10^5 (1/Ms) and 1.3 to 1.6 x 10^{-5} (1/s), respectively.

Study No. MIRACL-26808: Cross reactivity of humanized monoclonal antibody hP67.6 with tissues of Cynomolgus monkeys and Sprague-Dawley rats (GLP).

Biotinylated hP67.6 was applied to cryosections of Cynomolgus monkeys and Sprague-Dawley rat tissues at 7 and 72 mcg protein/mL. Specific staining with hP67.6 was not apparent in monkey or rat tissues. Nonspecific background staining included intestine, renal tubular epithelium, parenchyma, fat, collagen and/or muscle. Nonspecific moderate to intense background staining observed in mast cells, eosinophils and tissue macrophages in all tissues sections. The strong staining of some tissues was noted but

was considered negative on the basis that either: a) labeling was cytoplasmic rather than on the plasma membrane, b) other sections of the same sample were negative, c) positive staining was also noted with the control antibody, biotinylated humanized IgG4.

(Summary Excerpted from NDA 21174 review)

CMA-676 demonstrated in vitro activity against the CD33-positive (CD33+) HL-60 human promyelocytic leukemia cell line. CMA-676 was very potent and demonstrated high selectivity for CD33+ target cells relative to CD33- control cells. The unconjugated NAc-gamma calicheamicin DMH was much less cytotoxic to target cells than the conjugate but had comparable potency toward both the target and control cells lines. CMA-676 was 1000-fold more cytotoxic to HL-60 cells than a comparable conjugate made with a non-targeting control antibody, and the unconjugated hP67.6 antibody showed no cytotoxicity in this assay. The cytotoxic effects of CMA-676 were also investigated in HL-60, NOMO-1, N134, NKM-1 (all CD33 positive), KS62 (weakly positive), and Daudi (CD33 negative) cells. Concentration-dependent, selective cytotoxicity was observed using flow cytometry to measure cell viability with the CD33 positive cell lines. Sensitive cells were temporally arrested at the G2/M phase of the cell cycle, except for NKM-I cells. For the HL-60 cell line, morphological examination and DNA-fragmentation assays indicated that the primary cytotoxic effect of CMA-676 may be necrotic rather than apoptotic.

In vivo antitumor effects of CMA-676 were studied in an HL-60 xenograft tumor model. CMA-676 showed a dose-response effect with >80% inhibition of tumor growth at doses between 0.8 and 2.4 mg/m^2 NAc-gamma calicheamicin DMH equivalents (36 to 108 mg protein/m^2). Significant increases in mortality occurred at the maximum dose studied of 3.2 mg/m^2. At the lowest dosage of 0.8 mg/m^2, significant reduction of tumor growth was observed with no deaths, and 2 of 5 animals were tumor free at day 37. The doses used in the xenograft model described above (36 to 108 mg protein/m^2) were much higher than the doses used in clinical trials (0.25 to 9 mg protein/m^2) at least in part because the subcutaneously implanted HL-60 leukemia grows as a solid tumor. It is likely that significantly higher doses were required in the xenograft model because solid tumors are targeted much less efficiently than naturally occurring leukemias.

4.2 Secondary Pharmacology

Previously reviewed. No evidence of hemolysis or protein flocculation was found

4.3 Safety Pharmacology

Gemtuzumab ozogamicin was evaluated for potential effects on nervous, cardiovascular, gastrointestinal, hepatic, and renal systems in vivo and/or in vitro. In addition, an in vitro hERG current inhibition assay was conducted with N-Ac-□-calicheamicin DMH.

Table 3 Outline of Safety Pharmacology Testing

(Excerpted from Submission)

Study Type and Duration[a]	Route of Administration	Test System	Compound Administered
In Vitro Studies			
Effect of N-Ac-γ-Calicheamicin DMH on the hERG Potassium Current Stably Expressed in HEK293 Cells	In Vitro	HEK293 cells stably expressing hERG	PF-06649266[b]
Effect of Gemtuzumab Ozogamicin on Autonomic Nervous System and Smooth Muscle	In Vitro	Freshly isolated guinea pig ileum	PF-05208747[c]
In Vivo Studies[d]			
Central Nervous System, General Activity and Behavior	IV	Mouse/ICR	PF-05208747[c]
Digestive System	IV	Mouse/ICR	PF-05208747[c]
Kidney Function	IV	Mouse/ICR	PF-05208747[c]
Hepatic Function	IV	Rat/ Sprague-Dawley	PF-05208747[c]
Cardiovascular – Conscious Dog	IV	Dog/ Beagle	PF-05208747[c]

DMH = Dimethylhydrazide; GLP = Good Laboratory Practice; HEK = Human embryonic kidney; hERG = Human ether-à-go-go-related gene; ICR = Imprinting control region; IV = Intravenous; N-Ac = N-Acetyl.
a. All studies were conducted non-GLP.
b. Also referred to as CL 184,538.
c. Also referred to as CMA-676, CL 555,201, or Mylotarg®.
d. Single-dose, IV.

Summary of Findings

In vitro hERG Assessment with N-Ac-Gamma-Calicheamicin-DMH:
N-Ac-ɣ-calicheamicin DMH was tested at concentrations of 1, 3, and 6.77 mcM. Less than 1% inhibition of mean hERG current amplitude was observed relative to vehicle control. The IC50 for the inhibitory effect of N-Ac-ɣ-calicheamicin DMH on hERG potassium channels was >6.77 mcM (10,000 ng/mL).

Central Nervous System, Mice and Rats
Gemtuzumab ozogamicin was administered to male mice as a single bolus IV dose at doses of 3, 9, 30, or 90 mg/m^2. No noticeable changes in gross activity and behavior of mice, or on the pain threshold in the hot plate test or effects on body temperature.

Study No. MIRACL-26834: Cardiovascular Safety Assessment of CL 555,201 in Conscious Beagle Dogs

Excerpted from NDA review:

Species:	beagle dogs (2/sex/group)
Age:	10-26 months
Weight:	10.5-13.3 kg
Drug:	hP67.6 conjugate
Dosage- hP67.6 equivalents:	4, 13, 40 mg/m^2 (compared to vehicle in same animal on previous day)
Toxic equivalents:	100, 330, 1000 mcg/m^2 NAc-calicheamicin AcBut (191,305)
Route:	i.v. 30 min infusion except 40 mg/m^2 was bolus
Observation:	-30 min prior to -60 min post dosing

dose	mean arterial pressure	heart rate	cardiac output	ECG
4 mg/m^2	5%↓at 55, 85 min	-	10%↓at 50 min	-
13	↓ trend (10%) 25-60 min	40% ↑ at all times ≥ 15 min	-	P-wave amplitude ↑ 30% at 20-60 min; T-wave amplitudes ↑ 45-140% at all times≥ 15 min
40	~20%↓ at 5-25 min	rising trend 15-60 min	40%↓ 5-10 min	P-wave ↑ trend at 5 min w/ sign. at 40 min only (25%); 160% ↑ T-wave 5-45 min

Single IV doses of gemtuzumab ozogamicin were associated with reductions in mean arterial blood pressure, increases in heart rate and increases in P- and T-wave amplitude at ≥13 mg/m^2.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Previously reviewed
Summary of Findings:

The pharmacokinetic parameters for the drug substance, hP67.6 conjugate, are shown in Table 4. Very little dissociation of calicheamicin occurred in vivo. The half-life was very long (3-7 days) as appropriate for an immunoglobulin. The half-life in monkeys was much greater than in rodents.

Calicheamicin analogues had half-lives of approximately 18 hr in rats and dogs. The addition of the AcBut linker to the DMH derivative elevated the C_{max} and AUC approximately 20- and 10-fold. A dose of 1000 mcg/kg of 184,538, which was non-lethal to rats, produced a plasma concentration that was 10-20-fold higher than the 1 hr

IC_{50} against HL-60 cells. Possible gender-based differences in the pharmacokinetics were noted.

Table 4 Pharmacokinetic Parameters of hP67.6 Conjugate

(Excerpted from NDA Review)

Study #	species	dose µg/kg	C_{max} µg/ml		AUC µg•hr/ml		$t_{½}$ hr		% Free (time) calicheamicin
			Total drug	MoAb	Total drug	MoAb	Total drug	MoAb	
89	rat	1600	1.14	-	19.6	-	81	-	<2 (120 hr)
90	monkey	1300	1.58	-	37.9	-	141	-	<2 (120 hr)
63	rat	1200	0.494	31.7	8.78	1180	39	72	3.6
64	monkey	1800	1.49	3.57	25.7	2530	183	176	0.8
65	chimp	42[a]	7.97		-		-		-

5.2 Toxicokinetics

See repeat-dose toxicology studies

6 General Toxicology

6.1 Single-Dose Toxicity

Studies previously reviewed:

- Study MIRACL-26711 (94033): An exploratory single dose intravenous tolerance study of CL 555,201 (N-acetyl-gamma-dimethyl-hydrazide-acetyl-butyryloxy derivative of calicheamicin (CL 191,305) conjugated to hP67.6 [CL 555,001)), an anticancer agent, in rats.

- Study MIRACL-26710 (93214): A single dose intravenous toxicity study of CL 555,201 (N-acetyl-gamma-dimethyl-hydrazide-- acetyl-butyryloxy derivative or calicheamicin (CL 191,305] conjugated to hP67.6 (CL 555,001]), an anticancer agent, in male monkeys.

Summary of Findings

Single dose studies were conducted in rats and monkeys. The LD_{10} was between 8.4 and 12 mg/m^2 in rats, and between 36 and 54 mg/m^2 in monkeys. In rats and monkeys the primary toxicities were predominantly to the liver, kidney, spleen, lungs, and GI tract. The toxicity data for various free calicheamicin derivatives is summarized in the table below.

Table 5 Calicheamicin Derivatives Toxicology Summary

(Excerpted from NDA Review)

Compound	species	LD_{10} µg/kg	LD_{10} µg/m2	target toxicities
184,538 NAc-calicheamicin DMH	mice	>500	>1500	hepato
184,538 NAc-calicheamicin DMH	rat	100<>300	600<>1800	hepato, nephro, myelo, gastric
164,538 NAc-calicheamicin DMH	dog	dose which when doubled did not kill the dogs was	250 µg/m² 12.5 µg/kg	nephro, myelo, GI,
191,305 NAc-calicheamicin DMH AcBut	rat	100<>300	600<>1800	hepato, nephro, myelo, gastric
190,396 NAc-ϵ-calicheamicin	rat	>1000	>6000	-

6.2 Repeat-Dose Toxicity

Studies previously reviewed:
Study MIRACL-26813 (94034): Six Cycle intravenous toxicity study of CL 555,201 (N-acetyl-gamma-dimethyl-hydrazide-acetyl-butyryloxy derivative of calicheamicin [CL 191,305] conjugated to hP67.6 (CL 555,001]), an anticancer agent, in rats followed by a four week recovery period.

Summary of Findings
Rats were administered 6 weekly doses at 0 (PBS control), 7.2 (hP67.6 antibody control), or CL 555,201 (gemtuzumab ozogamicin) at doses of 0.6, 2.4, or 7.2 mg/m^2/week and observed for an additional 4 weeks. CL 555,201-related hematologic effects occurred on red blood cell mass (RBC, hemoglobin, and hematocrit), and WBC counts. Primary CL 555,201-related microscopic findings in rats were observed mostly in ≥2.4 mg/m^2/week rats in the kidney, liver, spleen, bone marrow, testes/epididymides, and male mammary gland. Effects on the male mammary gland, kidney, liver and testes/epididymides were still present at the end of the 4-week recovery period. ADA were detected to total hP67.6 antibody on Days 21, 41, and 65 in animals given hP67.6 antibody alone or ≥0.6 mg/m^2/week CL 555,201 and it was responsible for the decreased exposures. The NOAEL was defined at 0.6 mg/m^2/week based on adverse effects on male reproductive organs, kidney, liver, bone marrow, and spleen at ≥2.4 mg/m^2/week. The mean C_{max} exposure value for total hP67.6 antibody after the first dose was 1840 ng/mL and the mean AUC_{168} exposure value for total hP67.6 antibody after the first dose was 90,600 ng•h/mL at 0.6 mg/m^2/week.

Study MIRACL-26812 (94001): Six Cycle intravenous toxicity study of CL 555,101 (N-acetyl-gamma-dimethyl-hydrazide-acetyl-butyryloxy derivative of calicheamicin [CL 191,305] conjugated to hP67.6 (CL 555,001]), an anticancer agent, in monkeys followed by a four week recovery period.

Summary of Findings
Monkeys were administered 6 weekly IV doses at 0 (PBS control), 22 (hP67.6 antibody control), or CL 555,201 (gemtuzumab ozogamicin) at doses of 2.4, 7.2, or 22 mg/m^2/week (5, 15 or 45 mcg/kg/week calicheamicin equivalents) and observed for an additional 4 weeks. CL 555,201-dose-related hematologic effects occurred at ≥7.2

mg/m^2/week that included lower RBC mass (11% to 42%), WBCs (5% to 68%), polymorphonuclear cells (33% to 78%), and lymphocytes (41% to 63%). CL 555,201-related clinical chemistry effects occurred at ≥2.4 mg/m^2/week on Days 9 and/or 37 and consisted of higher AST, total protein, globulin, and sodium, and lower albumin and albumin/globulin ratio (A/G). Primary CL 555,201-related microscopic findings in monkeys were observed mostly in ≥7.2 mg/m^2/week in the kidney, liver, thymus, spleen, lymphatic tissues, and bone marrow. One to 3 animals in each group given hP67.6 antibody or CL 555,201 tested positive for ADA to total hP67.6. The impact of ADA on systemic exposure at the end of the dosing period is not known because toxicokinetic parameters were not calculated. The NOAEL was defined at 2.4 mg/m^2/week based on target organ toxicity in the kidney, liver, and lympho-hematopoietic organs at ≥7.2 mg/m^2/week. Mean C_{max} and AUC_{168} exposure values (males and females combined) for CL 555,201 (as measured by total hP67.6 antibody) at week 1 (data for week 6 was not collected) were 3500 ng/mL and 258,000 ng•h/mL, respectively at 2.4 mg/m^2/week.

A summary of findings from previously reviewed rat and monkey six cycle repeat-dose toxicity studies indicate that hP67.6 conjugate at high doses is hepatotoxic, nephrotoxic, and myelotoxic, see Table 6.

Table 6 Summary of Findings in Rat and Monkey Six Cycle Repeat-Dose Toxicology Studies

(Excerpted from NDA Review)

	HD mg/m²	Clinical Chemistry	Hematology	Gross Pathology	Histopathology
rat	7.2 x 6	cholesterol, AST, ALT, AP, albumin, globulin, A/G, total protein, triglycerides, glucose, proteinuria	RBC, WBC, lymphocytes, platelets	discolored/rough liver, pale kidneys, small testes	liver- atrophy, karyocytomegaly, vacuolation, oval cell/bile duct proliferation; kidney- tubular dilation, basophilia; testes- atrophy
monkey	21.6 x 6	AAT, ALT, albumin, globulin, A/G, total protein, BUN, creatinine, proteinuria	RBC, Ht, Hg, MCV, MCHb WBC, lymphocytes	red liver foci, small thymus, gelatinous bone marrow	liver- atrophy, pigmented Kupffer cells, dilation of sinusoids, single cell necrosis; kidney- tubular dilation, basophilia, casts, eosinophilic material, vacuolation; lymphoreticular- lymphocyte depletion in thymus, spleen, lymph nodes, and tonsils; hypocellular marrow

Study title: CMA-676: Six cycle intravenous comparative toxicity study in male monkeys

Study no.:	GRT-27677
Study report location:	eCTD 4.2.3.2
Conducting laboratory and location:	Wyeth-Ayerst Research Drug Safety Chazy, NY
Date of study initiation:	January 5, 1996
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	CMA-676 Conjugate from new cell line Lot # 4489A-35-301195-R1592-163 Protein content: 5.25 mg/vial, Total calicheamicin derivatives: 33.9 mcg/mg of protein CMA-676 Conjugate from old cell line Lot # 4489A-24-102593-R1592-24 Protein content: 5.45 mg/vial, Total calicheamicin derivatives: 27 mcg/mg of protein

Key Study Findings

- Decreases in red cell mass in the 45 mcg/kg (new cell line) considered as a mild non-regenerative anemia. Marked eosinophilia occurred at all dose levels and was associated with hypersensitivity reactions in few monkeys dosed with the old cell line.
- Increases in ALT, AST, TP, GLOB, TRIG and decreases in AP and A/G with no microscopic correlates.
- Target organs for CMA-676 toxicity included the bone marrow, kidneys, liver, skeletal muscle, spleen, thymus and testes.
- Decreases in absolute and adjusted liver, pituitary, testes and thymus organ weights. Microscopic correlates included degeneration of seminiferous tubules and lymphoid depletion in testes and thymus.
- Antibody response to hP67.6 or to calicheamicin was detected in 8/19 or 3/18 monkeys in the low- and mid-dose.
- Similar toxicological and systemic exposure profile between the old and new cell lines

Methods

Doses:	Control saline, control antibody new cell line, 15 mcg/kg Old cell line or 5, 15 or 45 mcg/kg New cell line (calicheamicin equivalents)
Frequency of dosing:	Weekly
Route of administration:	IV
Dose volume:	0.15 to 1.62 mL/kg
Formulation/Vehicle:	Saline or hP67.6 antibody without the calicheamicin derivative in sucrose, sodium chloride, sodium phosphate, and dextran
Species/Strain:	Cynomolgus monkeys
Number/Sex/Group:	3 males/group
Age:	29 to 50 months (2.4 to 4.2 years old)
Weight:	2.5 kg to 3.9 kg
Satellite groups:	none
Unique study design:	Males only. Doses matched doses used in Study MIRACL-26812 (94001)
Deviation from study protocol:	Deviations had no impact on study results or data interpretation

Observations

Table 7 Experimental Design for Bridging Comparative Toxicology Study of CMA-676 in Monkeys

(Excerpted from Submission)

DOSAGE GROUP		DOSAGE[a] (mcg/kg/day)	CONCEN-TRATION mcg calicheamicin/mL	DOSE VOLUMES mL/kg	ANIMAL NUMBER MALE
I	Vehicle-Control (Saline)	0	0	1.62	1-3
II	Antibody Control (New Cell Line)	0	0	1.62	4-6
III	Middle (Old Cell Line)	15	29.1	0.52	7-9
IV	Low (New Cell Line)	5	32.7	0.15	10-12
V	Middle (New Cell Line)	15	32.7	0.46	13-15
VI	High (New Cell Line)	45	32.7	1.38	16-18

a: Dosages were based on the concentration of calicheamicin for Groups III - VI. Group II animals were dosed based on an equivalent amount of protein as Group VI. Group I was dosed based on the highest dose volume given (Group II).

Note: The protein content of the new cell line (Groups IV, V, VI) is 1 mg protein/30.5 mcg calicheamicin or 1.07 mg protein/mL. The protein content of the old cell line (Group III) is 1 mg protein/25.9 mcg calicheamicin or 1.12 mg protein/mL. The protein content of Antibody Control (Group II) is 0.91 mg/mL.

Results

Mortality

None

Clinical Signs

CMA-676-related rash occurred in two males dosed with the old cell line at 15 mcg/kg and one male dosed with the new cell line at 45 mcg/kg. The rash appeared after the second or third dose and lasted for 30-37 days suggesting sensitization to CMA-676.

Body Weights

Unremarkable

Feed Consumption

Unremarkable

Ophthalmoscopy

Unremarkable

ECG

Not conducted

Hematology

CMA-676-related decrease (>25%) in red cell mass in the 45 mcg/kg new cell line group can be considered as a mild anemia. There was no reticulocytes response suggesting the anemia was nonregenerative. Dose-related decreases in white blood cells were accompanied by decreases in lymphocyte and increases in neutrophils at all dose levels. Marked eosinophilia occurred at all dose levels. Eosinophilia in two males at 15 mcg/kg old cell line was associated with a rash and it may be considered a hypersensitivity reaction. Similar overall response observed with the old and new cell line at 15 mcg/kg.

Table 8 CMA-676-related Effects on Hematology Parameters

Parameter	NEW Cell Line CMA-676 (mcg/kg)			OLD Cell Line CMA-676 (mcg/kg)
	5	15	45	15
RBC	↑5.3	↓3.3	↓26.7	↓12.0
HGB	↑3.6	↓6.2	↓24.3	↓7.4
HCT	--	↓10.4	↓25.4	↓11.6
RET	↓31.2	↓8.2	↑12.5	↓64.4
WBC	↑17.1	↓25.4	↓60.1	↓34.0
LYM	↓10.9	↓37.7	↓37.3	↓27.8
NEU	↑31.7	↑141.7	↑85.0	↑66.7
EOS	↑166.5	↑66.5	↑533.5	↑433.5
PLAT	↓13.4	↓5.2	↓6.9	↓32.2

RBC: red blood cells. HGB: hemoglobin. HCT: hematocrit. RET: reticulocytes.
WBC: white blood cells. LYMP: lymphocytes. NEU: neutrophils. EOS: eosinophils

Clinical Chemistry

CMA-676-related increases in ALT, AST, TP, GLOB, TRIG and decreases in AP and A/G were small in magnitude with no microscopic correlates but these changes were present at all dose levels. Similar overall response observed with the old and new cell line at 15 mcg/kg.

Table 9 CMA-676-related Effects on Clinical Chemistry Parameters

Parameter	NEW Cell Line CMA-676 (mcg/kg)			OLD Cell Line CMA-676 (mcg/kg)
	5	15	45	15
ALT	↑58.2	↑87.7	↑85.7	↑51.0
AST	↑134.7	↑142.1	↑212.6	↑172.6
ALP	↓21.1	↓30.5	↓25.8	↓13.4
GLOB	↑19.4	↑34.5	↑51.6	↑25.8
A/G ratio	↓16.3	↓29.9	↓40.8	↓20.4
TP	106.2	110.9	114.1	110.9
TRIG	↓44.1	↓14.4	↓14.4	↓46.2

ALT: alanine aminotransferase. AST: aspartate aminotransferase.
ALP: alkaline phosphatase. GLOB: globulin. A/G ratio: albumin to globulin.
TP: total protein. TRIG: triglycerides.

Urinalysis

One 45 mcg/kg male had proteinuria during week 6 of the study with corresponding microscopic renal changes of slight, multi focal tubular dilatation near the cortico-medullary junction. Although the proteinuria was only in one monkey, proteinuria with renal changes was reported in a previous study with CMA-676 old cell line [Study MIRACL-26812 (94001)], and it is considered a CMA-676-related finding.

Gross Pathology

Focal, red discoloration at injection sites occurred in most of monkeys at all dose levels that corresponded microscopically with mild to moderate hemorrhage. Small thymus noted at 45 mcg/kg and at 15 mcg/kg-old cell line corresponded with moderate to marked lymphoid depletion.

Organ Weights

CMA-676-related significant decreases in absolute and adjusted liver, pituitary, testes and thymus weight occurred mostly in 45 mcg/kg males. Reductions in mean testicular and thymic weights corresponded with degeneration of seminiferous tubules and lymphoid depletion, respectively, in 45 mcg/kg monkeys.

Table 10 CMA-676-related Effects on Adjusted Organ Weight

Organ	NEW Cell Line CMA-676 (mcg/kg)			OLD Cell Line CMA-676 (mcg/kg)
	5	15	45	15
Liver	↑1.2	↓10.5	↓6.0	↓1.9
Pituitary	↓16.7	↓16.7	↓33.3	↓33.3
Prostate	↓17.3	--	↓26.9	↑3.8
Spleen	↑65.0	↓12.1	122.9	↑19.8
Testes	↑131.0	↑52.9	↓45.6	↑29.0
Thymus	↓19.2	↓67.5	↓90.7	↓45.1

Histopathology

Adequate Battery: Yes
Peer Review: Yes
Histological Findings:

Table 11 CMA-676-related Microscopic Findings in Monkeys

Organ	Controls		Old Cell Line	New Cell Line		
CMA-676 (mcg/kg)	0	0	15	5	15	45
Number of Animals in Group	3	3	3	3	3	3
Bone marrow						
Hypocellular			2	2	1	3
Kidneys						
Tubular dilation						1
Red granules						1
Liver						
Sinusoidal dilation						1
Single cell necrosis						1
Pericholangitis				1		
Lymph nodes						
Cervical and mesenteric atrophy germinal center						3
Lymphoid depletion			1			3
Prostate						
Immature	3	3	3	2	3	3
Skeletal muscle						
Hemorrhage		1		2	1	
Spleen						
Lymphoid depletion			2		2	3
Atrophy germinal centers			1			3
Testes						
Immature	3	3	3	2		
Tubular degeneration						3
Thymus						
Lymphoid depletion			1		1	3

Special Evaluation

Immunogenicity Evaluation
Plasma obtained from all animals once pretest and during week 6 was evaluated for

anti-hP67.6 antibodies and anti-calicheamicin antibodies by ELISA assay. Antibody response to hP67.6 or to calicheamicin was detected in 8/19 or 3/18 monkeys, respectively, assigned to the low- or mid-dose groups. Antibody responses were classified as probable or possible, the response was similar in both groups (old CMA-676 and new CMA-676) and these results were similar to historical data.

Toxicokinetics

Systemic exposure to CMA-676 conjugate, as measured by $AUC_{(0\text{-}168)}$, generally increased with increasing dose from 5 to 45 mcg/kg in both cycle 1 and 6. The increases in AUC were approximately proportional and values were higher after the sixth cycle indicating accumulation with repeated dosing. Half-life ranged from 127 to 267 hours. The mean (±SD) AUC values from monkeys receiving CMA-676 conjugate, using antibody derived from the old and the new cell lines, were similar during the first and sixth cycle. These data indicate that CMA-676 derived from old and new cell lines results in similar exposure to hP67.6.

Table 12 Mean Toxicokinetic Parameter of hP67.6 (antibody portion of CMA-676) from Monkey during the Six-cycle Comparative Toxicity Study

(Excerpted from Submission)

DOSAGE Calicheamicin (µg/kg)	DOSAGE Protein (mg/kg)	C(0-2) (µg/mL)	AUC(0-168) (µg*hr/mL)	AUCo-inf (µg*hr/mL)	TOTAL CLEARANCE (mL/hr/kg)	Vss (L/kg)	T½ (hr)
CYCLE # 1							
Control (new antibody cell line)							
0	1.47	33.2 ±3.5	2671 ±74	5263 (n=2)	0.280 (n=2)	0.0670 (n=2)	166 (n=2)
Conjugate (old antibody cell line)							
15	0.58	9.69 ±1.05	678 ±51	1273 ±150	0.460 ±0.057	0.101 ±0.006	155 ±10
Conjugate (new antibody cell line)							
5	0.16	3.46 ±0.56	201 ±29	332 ±37	0.487 ±0.056	0.088 ±0.016	127 ±9
Conjugate (new antibody cell line)							
15	0.49	10.8 ±0.5	670 ±73	1298 ±359	0.397 ±0.106	0.0865 ±0.0040	162 ±40
Conjugate (new antibody cell line)							
45	1.48	30.5 ±3.4	1785 ±42	3986 (n=2)	0.373 (n=2)	0.108 (n=2)	207 (n=2)
CYCLE # 6							
Control (new antibody cell line)							
0	1.47	66.0 ±4.4	6571 ±650	NA	0.225 ±0.022	0.128 ±0.021	187 ±21
Conjugate (old antibody cell line)							
15	0.58	19.6 ±2.3	1851 ±165	NA	0.315 ±0.027	1.44 ±1.87	218 (n=1)
Conjugate (new antibody cell line)							
5	0.16	4.86 ±1.40	475 ±89	NA	0.345 ±0.068	0.217 ±0.068	194 ±34
Conjugate (new antibody cell line)							
15	0.49	17.5 ±4.2	1605 ±296	NA	0.313 ±0.060	0.188 ±0.061	191 ±39
Conjugate (new antibody cell line)							
45	1.48	44.9 ±3.0	4086 ±150	NA	0.363 ±0.013	0.200 ±0.031	187 ±23

Note = C(0-2) and AUC values were calculated based on actual data.
C(0-2) = Concentration at first sampling time (taken between 0 to 2 minutes after IV dosing for individual monkeys)
NA = values not applicable

Dosing Solution Analysis

Analysis of the test articles prior to study initiation and at the end of the study showed that the materials were not within acceptable limits for select parameters, see Table 13. The Sponsor considered that the materials were fully characterized and both cell lines were acceptable for use.

Table 13 Dose Formulation Analysis

(Excerpted from Submission)

	Calicheamicin[a]	Protein[a]	µg Calicheamicin/ mg protein[b]
Old cell line	(b) (4) %	(b) (4) %	(b) (4)
New cell line	%	%	

a: % of claim

b: limits (b) (4) µg/mg

7 Genetic Toxicology

Study reports for bacterial mutagenicity and in vitro micronucleus test with N-Ac-ɣ-calicheamicin DMH were not reviewed but a brief summary is provided.

- N-Ac-ɣ-calicheamicin DMH was positive for mutagenic activity in the E. coli strain WP2 uvrA pKM101, with and without metabolic activation, and negative for mutagenic activity in the S. typhimurium strains TA98, TA100, TA1535, and TA1537 with and without metabolic activation under the conditions of the assay.

- N-Ac-ɣ-calicheamicin DMH was positive for inducing micronuclei in vitro in TK6 cells with and without metabolic activation under the conditions of the test system.

7.1 *In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)

Previously reviewed
Study No. GTR-28070: Mutagenicity test on CMA-676/Calicheamicin in an in vivo mouse micronucleus assay

Summary of Findings
CMA-676 is clastogenic in the in vivo mouse bone marrow micronucleus assay.

8 Carcinogenicity

No studies submitted or previously reviewed

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

Study title: CMA-676: Intravenous Female Fertility Study in Rats

Study no.:	40230
Study report location:	eCTD 4.2.3.5.1
Conducting laboratory and location:	Safety Assessment Research Medical Research Laboratories Wyeth Lederle Japan, Ltd. Saitama 353-8511 , Japan
Date of study initiation:	August 2, 1999
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	CMA-676; 050597PSG2024-14; 5 mg vial Protein content: 4.90 mg/vial, Total calicheamicin derivatives: 24.6 pg/mg of protein

Key Study Findings

- Significant decreases in mean body weight and food consumption during the dosing period at ≥0.06 mg/kg/day (0.36 mg/m^2/day) but not effects on mean body weight gain during GD 0-14
- Significant lower number of corpora lutea, implantations, and live fetuses occurred at 0.18 mg/kg/day (1.08 mg/m^2/day) in females mated at the end of the dosing period. A dose-related increase in dead fetuses with statistical significance at ≥0.06 mg/kg/day (0.36 mg/m^2/day).

Methods

Doses:	0, 0.02, 0.06, or 0.18 mg/kg/day 0, 0.12, 0.36, or 1.08 mg/m^2/day Dose levels selected based on a DRF in rats
Frequency of dosing:	Daily for 14 days
Dose volume:	1 mL/kg
Route of administration:	IV
Formulation/Vehicle:	Phosphate buffered saline supplemented with 1.0% rat serum albumin and 1.55% sucrose
Species/Strain:	Crj:CD(SD)IGS rats
Number/Sex/Group:	32 females/group
Satellite groups:	None
Study design:	Dosing during pre-mating period only
Deviation from study protocol:	None

Observations

Dose selection: In a preliminary study, decreases in maternal body weight gains and the number of live fetuses were observed in dams given 0.06 mg/kg/day and above. Therefore, dosage of 0.18 mg/kg/day was selected as the highest dose level of this study and dosages of 0.06 and 0.02 mg/kg/day were selected as the intermediate and lowest dose levels, respectively, in common ratio of 3.

Table 14 Experimental Design Female Fertility Study

(Excerpted from Submission)

Group	Dose[a)] (mg/kg/day)	Concentration (mg/mL)	Dose Volume (mL/kg)	No. of Animal		Animal No.
				Total	Recovery	
Control	0	0	1	32	16	401~416, 417~432[b)]
CMA-676	0.02	0.02	1	32	16	433~448, 449~464[b)]
CMA-676	0.06	0.06	1	32	16	465~480, 481~496[b)]
CMA-676	0.18	0.18	1	32	16	497~512, 513~528[b)]

a) : Dosages are expressed as total quantity of the hP67.6 antibody and calichemicin conjugate. Dosages of the hP67.6 antibody are 0.020, 0.059, and 0.176 mg/kg/day, and dosages of the calichemicin are 0.48, 1.44, and 4.32 μg/kg/day in the 0.02, 0.06, and 0.18 mg/kg groups of CMA-676, respectively. Dosing concentration analyses of the low, middle and high dose groups of CMA-676 were based on 0.020, 0.059 and 0.176 mg/mL of protein antibody concentration.

b) : Animals for the recovery study for 6 weeks.

Mating: 16 females/group mated with untreated males after 14-day dosing; 16 females/group underwent 6-weeks recovery before mating with untreated males. Cohabitation conducted overnight one-on-one basis for 5 days. Successful copulation was confirmed by the presence of vaginal plug or sperm in the vaginal smear in the next morning, and the day of successful copulation was designated as day 0 of gestation (GD0).

Reproductive ability: days required for successful copulation.
Copulation index (number of copulated animals/number of mated animalsx100)
Female fertility index (number of pregnant females/number of copulated femalesx100)

Hysterectomy: conducted on GD14.
Numbers of corpora lutea, implants, and dead and live embryos were counted
Pre-implant loss index [(number of corpora lutea - number of implants) /number of corpora lutea]
Dead embryo index (number of dead embryos/number of implantsx100)

Results

Mortality

None

Clinical Signs

Unremarkable

Body Weight

CMA-676-related significant decreased in mean body weight and body weight gain of females during the dosing period occurred at 0.06 and 0.18 mg/kg/day that corresponded with significant lower food consumption in both dosing groups, see Table 15 and Table 21. The significant lower body weight was present in all female rats during the recovery and gestation day periods for rats mated at the end of dosing and recovery period, respectively, see tables below. Food consumption was similar to control groups at different intervals during the gestation periods that resulted in similar mean body weight gain of female rats in CMA-676 groups compared to control, see Table 18 and Table 20.

Table 15 Mean Body Weight of Female Rats Dosed with CMA-676 before Mating

(Excerpted from Submission)

Group and dose		Control			0.02 mg/kg			0.06 mg/kg			0.18 mg/kg		
		Body weight (g)											
Days of study	0	254.2±	10.0	(32)	254.5±	10.5	(32)	254.9±	10.1	(32)	252.1±	8.9	(32)
	3	259.1±	9.5	(32)	258.2±	10.0	(32)	255.5±	10.6	(32)	249.2±	10.5**	(32)
	7	266.4±	11.3	(32)	263.0±	11.0	(32)	257.8±	9.9**	(32)	246.3±	10.5**	(32)
	10	270.1±	11.5	(32)	266.2±	11.5	(32)	258.9±	10.2**	(32)	244.2±	12.2**	(32)
	14	276.2±	13.6	(32)	271.3±	14.4	(32)	261.9±	10.5**	(32)	244.6±	11.7**	(32)
Body weight gain (Day 0- 14)		22.0±	8.4	(32)	19.8±	8.7	(32)	10.0±	7.3**	(32)	-7.5±	7.6**	(32)

**: P<0.01 (significantly different from control).
Values are mean±S.D. and the values in parentheses represent the number of animals.

Table 16 Mean Body Weight of Female Rats during the Recovery Period of 6-weeks

(Excerpted from Submission)

Group and dose		Control			0.02 mg/kg			0.06 mg/kg			0.18 mg/kg		
		Body weight (g)											
Days of study	21	293.8±	13.1	(16)	284.9±	7.5	(16)	274.3±	10.6**	(16)	262.9±	11.0**	(16)
	28	306.5±	12.0	(16)	295.6±	8.2*	(16)	287.5±	13.4**	(16)	275.6±	9.1**	(16)
	35	316.5±	10.6	(16)	310.3±	10.8	(16)	301.4±	15.6**	(16)	286.5±	10.0**	(16)
	42	323.5±	14.4	(16)	317.5±	14.3	(16)	306.3±	18.9**	(16)	292.9±	10.0**	(16)
	49	334.4±	16.7	(16)	329.7±	13.3	(16)	316.5±	22.2	(16)	302.1±	11.1**	(16)
	56	343.3±	17.1	(16)	336.6±	14.3	(16)	325.7±	23.1*	(16)	308.6±	11.4**	(16)
Body weight gain (Day 14- 56)		65.6±	10.4	(16)	69.0±	14.0	(16)	65.9±	20.4	(16)	64.7±	12.3	(16)

*: P<0.05, **: P<0.01 (significantly different from control).
Values are mean±S.D. and the values in parentheses represent the number of animals.

Table 17 Mean Body Weight of Female Rats during Pregnancy GD0-14 – Mated Group at the end of Dosing

(Excerpted from Submission)

Group and dose		Control			0.02 mg/kg			0.06 mg/kg			0.18 mg/kg		
		Body weight (g)											
Days of gestation	0	283.8±	16.0	(15)	279.8±	13.4	(15)	269.2±	15.5*	(14)	253.5±	14.3**	(16)
	3	303.1±	14.4	(15)	298.0±	14.7	(15)	286.9±	13.4*	(14)	272.6±	15.9**	(16)
	6	319.7±	13.7	(15)	312.7±	14.7	(15)	301.0±	16.5**	(14)	286.6±	12.3**	(16)
	9	332.8±	13.9	(15)	324.0±	16.4	(15)	314.0±	17.1**	(14)	301.8±	16.7**	(16)
	12	348.5±	14.1	(15)	341.7±	18.0	(15)	333.7±	18.4	(14)	318.6±	16.0**	(16)
	14	360.2±	16.8	(15)	352.4±	19.9	(15)	342.9±	17.6*	(14)	325.9±	18.1**	(16)
Body weight gain (Day 0- 14)		76.4±	14.1	(15)	72.6±	10.0	(15)	73.7±	10.2	(14)	72.4±	11.5	(16)

*: P<0.05, **: P<0.01 (significantly different from control).
Values are mean±S.D. and the values in parentheses represent the number of dams.
Three animals(0.02 mg/kg: 1 and 0.06 mg/kg: 2) were non-pregnant.
One animal(Control: 1) did not copulate.

Table 18 Body Weight Gain of Female Rats during Pregnancy GD0-14 – Mated Group at the end of Dosing

Group and Dose (mg/kg/day)	0	0.02	0.06	0.18
GD 0-14	76.4	72.6	73.7	72.4
Percent Compared to Control	--	95	97	95

Table 19 Mean Body Weight of Female Rats during Pregnancy GD0-14 – Mated Group at the end of Recovery

(Excerpted from Submission)

Group and dose		Control			0.02 mg/kg			0.06 mg/kg			0.18 mg/kg		
								Body weight (g)					
Days of gestation	0	335.6±	12.8	(12)	334.4±	17.0	(14)	321.2±	22.6	(16)	302.9±	10.9**	(14)
	3	352.3±	11.6	(12)	351.0±	16.2	(14)	337.5±	24.1	(16)	320.0±	11.1**	(14)
	6	365.4±	12.1	(12)	362.3±	15.2	(14)	347.3±	23.7*	(16)	330.4±	10.4**	(14)
	9	373.9±	12.5	(12)	374.5±	17.0	(14)	357.4±	25.2	(16)	340.8±	9.7**	(14)
	12	389.5±	13.1	(12)	390.1±	14.8	(14)	371.9±	26.0*	(16)	356.4±	12.1**	(14)
	14	409.5±	13.5	(12)	397.5±	15.3	(14)	381.8±	25.5*	(16)	365.0±	10.6**	(14)
Body weight gain (Day 0- 14)		64.9±	12.8	(12)	63.1±	7.2	(14)	60.6±	5.8	(16)	62.0±	5.9	(14)

*: P<0.05, **: P<0.01 (significantly different from control).
Values are mean±S.D. and the values in parentheses represent the number of dams.
Two animals (0.02 mg/kg: 1 and 0.18 mg/kg: 1) were non-pregnant.
Six animals (Control: 4, 0.02 mg/kg: 1 and 0.18 mg/kg: 1) did not copulate.

Table 20 Body Weight Gain of Female Rats during Pregnancy GD0-14 – Mated Group at the end of Recovery

Group and Dose (mg/kg/day)	0	0.02	0.06	0.18
GD 0-14	64.9	63.1	60.6	62.1
Percent Compared to Control	--	97	93	96

Food Consumption

Table 21 Mean Food Consumption of Female Rats Dosed with CMA-676 before Mating

(Excerpted from Submission)

Group and dose		Control			0.02 mg/kg			0.06 mg/kg			0.18 mg/kg		
								Food consumption (g/day/rat)					
Days of study	0-7	19.3±	1.4	(32)	19.0±	1.4	(32)	16.9±	1.4**	(32)	14.7±	1.6**	(32)
	7-14	19.8±	1.3	(32)	19.3±	1.5	(32)	16.7±	1.6**	(32)	15.2±	2.5**	(32)

**: P<0.01 (significantly different from control).
Values are mean±S.D. and the values in parentheses represent the number of animals.

Table 22 Mean Food Consumption of Female Rats during the Recovery Period of 6-weeks

(Excerpted from Submission)

Group and dose		Control			0.02 mg/kg			0.06 mg/kg			0.18 mg/kg		
		Food consumption (g/day/rat)											
Days of study	14-21	20.9±	1.4	(16)	20.8±	1.4	(16)	19.0±	1.5**	(16)	19.5±	3.7**	(16)
	21-28	20.9±	1.2	(16)	21.4±	1.7	(16)	20.1±	2.3	(16)	19.7±	1.8	(16)
	28-35	21.3±	2.2	(16)	21.6±	1.7	(16)	20.3±	2.2	(16)	19.6±	2.1	(16)
	35-42	20.9±	1.4	(16)	21.7±	1.5	(16)	20.1±	2.1	(16)	19.6±	1.3	(16)
	42-49	21.0±	1.6	(16)	21.1±	1.6	(16)	20.4±	2.0	(16)	19.3±	1.1*	(16)
	49-56	20.6±	1.6	(16)	20.9±	1.6	(16)	20.3±	2.0	(16)	19.1±	1.1*	(16)

*: P<0.05, **: P<0.01 (significantly different from control).
Values are mean±S.D. and the values in parentheses represent the number of animals.

Table 23 Mean Food Consumption of Female Rats during Pregnancy GD0-14 – Mated Group at the end of Dosing

(Excerpted from Submission)

Group and dose		Control			0.02 mg/kg			0.06 mg/kg			0.18 mg/kg		
		Food consumption (g/day/rat)											
Days of gestation	0-3	23.7±	2.1	(15)	23.6±	1.6	(15)	21.1±	1.8**	(14)	21.1±	2.8**	(16)
	3-6	26.1±	2.5	(15)	25.2±	2.1	(15)	23.5±	2.1*	(14)	23.3±	3.0**	(16)
	6-9	26.7±	2.5	(15)	25.4±	2.1	(15)	24.6±	1.7*	(14)	24.3±	1.6**	(16)
	9-12	26.4±	2.8	(15)	25.9±	2.0	(15)	25.0±	1.7	(14)	24.5±	2.8	(16)
	12-14	25.0±	1.9	(15)	24.7±	2.0	(15)	24.8±	2.4	(14)	24.2±	2.7	(16)

*: P<0.05, **: P<0.01 (significantly different from control).
Values are mean±S.D. and the values in parentheses represent the number of dams.
Three animals (0.02 mg/kg: 1 and 0.06 mg/kg: 2) were non-pregnant.
One animal (Control: 1) did not copulate.

Table 24 Mean Food Consumption of Female Rats during Pregnancy GD0-14 – Mated Group at the end of Recovery

(Excerpted from Submission)

Group and dose		Control			0.02 mg/kg			0.06 mg/kg			0.18 mg/kg		
		Food consumption (g/day/rat)											
Days of gestation	0-3	21.0±	1.9	(12)	21.7±	2.3	(14)	20.6±	1.6	(16)	20.0±	1.6	(14)
	3-6	24.2±	2.6	(12)	24.9±	2.0	(14)	22.9±	1.9	(16)	23.0±	1.4	(14)
	6-9	24.6±	2.6	(12)	25.5±	1.9	(14)	23.5±	1.8	(16)	23.1±	1.3	(14)
	9-12	25.8±	2.6	(12)	25.9±	1.8	(14)	24.5±	1.7	(16)	24.2±	1.6	(14)
	12-14	25.1±	2.8	(12)	24.7±	1.9	(14)	23.3±	2.4	(16)	23.6±	1.4	(14)

Not significantly different from control.
Values are mean±S.D. and the values in parentheses represent the number of dams.
Two animals (0.02 mg/kg: 1 and 0.18 mg/kg: 1) were non-pregnant.
Six animals (Control: 4, 0.02 mg/kg: 1 and 0.18 mg/kg: 1) did not copulate.

Toxicokinetics

Toxicokinetics was previously evaluated in a rat EFD study, see Table 25.

Table 25 Toxicokinetic Parameters of CMA-676 in Gravid Rats given IV daily doses from GD 6-17

(Excerpted from Submission)

Dose (mg/kg/day)	$C_{2\ hours}$ (µg/mL)	AUC_{0-24} (µg•hr/mL)	AUC_{0-24}/Dose	CL_T (mL/min/kg)
0.025	1.64	30.6	1225	0.0136
0.075	5.84	124	1656	0.0101
0.2	17.5	346	1729	0.00964

Dosing Solution Analysis

CMA-676 is a white powder, and has been confirmed to be stable for (b) (4) -month in a refrigerator under the dark. CMA-676 dosing solution was prepared immediately before use. The concentrations of CMA-676 in mixture were measured at the first and final preparations and the concentrations were within acceptable limits (variation within ±25%), see Table 26.

Table 26 CMA-676 Formulation Analysis in the Female Fertility Study

(Excerpted from Submission)

First Preparation

Nominal CMA-676 concentration(mg/mL)	Nominal protein concentration(mg/mL)	Measured protein concentration(mg/mL)	Percentage to nominal protein Concentration (%)
0.02	0.01952	0.01976	101.2
0.06	0.05856	0.05888	100.5
0.18	0.17568	0.17952	102.2

Last Preparation

Nominal CMA-676 concentration(mg/mL)	Nominal protein concentration(mg/mL)	Measured protein concentration(mg/mL)	Percentage to nominal protein Concentration (%)
0.02	0.01952	0.01956	100.2
0.06	0.05856	0.06160	105.2
0.18	0.17568	0.16864	96.0

Necropsy

Unremarkable

Female Reproductive Ability

No CMA-676-related effects in the number of days required for successful copulation or effects in copulation and female fertility indices for rats mated at the end of the dosing or recovery period, see Table 27 and Table 28.

Hysterectomy Evaluations

The reproductive tract was dissected from the abdominal cavity, opened, and contents examined. Significant CMA-676-related effects occurred in hysterectomy evaluations for dams mated at the end of the dosing period at 0.18 mg/kg/day with decreased in the number of corpora lutea per liter, implantations and live fetuses and increased number

of dead fetuses. The number of live and dead fetuses was also significantly different at 0.06 mg/kg/day compared to control. Non-significant decreases in the number of corpora lutea per liter, implantations and live fetuses and increased number of dead fetuses also occurred at lower doses. No CMA-676-related effects in hysterectomy evaluations for dams mated at the end of the recovery period, see Table 28.

Table 27 Fertility Parameters of Female Rats Mated Group at the end of Dosing

Dose (mg/kg/day)	0	0.02	0.06	0.18
Number of females tested	16	16	16	16
Number of copulated females	15	16	16	16
Number of females pregnant	15 (100)	15 (93.8)	14 (87.5)	16 (100)
Duration of mating (mean days ± SD)	2.40 ± 1.24	2.38 ± 1.09	2.50 ± 1.10	2.75 ± 1.13
Unscheduled euthanasia	0	0	0	0
Number of surviving pregnant females	15	15	14	16
Corpora lutea Mean number per liter ± SD	244 16.27 ± 0.80	222 14.80 ± 2.73	208 14.86 ± 1.75	227 14.19 ± 1.52**
Implantations Mean number per liter	230 15.33 ± 1.05	213 14.20 ± 2.73	197 14.07 ± 2.09	219 13.69 ± 1.14**
Pre-implantation loss Percent to the # of corpora lutea	14 5.74	9 4.05	11 5.29	8 3.52
Live fetuses Percent to the # of corpora lutea	215 14.33 ± 1.40	196 13.07 ± 2.63	166 11.86 ± 2.32*	114 7.13 ± 2.45**
Dead fetuses Percent to the # of implants	15 6.52	17 7.98	31 15.74*	105 47.95**

Table 28 Fertility Parameters of Female Rats Mated Group at the end of Recovery

Dose (mg/kg/day)	0	0.02	0.06	0.18
Number of females tested	16	16	16	16
Number of copulated females (%)	12	15	16	15
Number of females pregnant	12 (100)	14 (93.3)	16 (100)	14 (93.3)
Duration of mating (mean days ± SD)	1.83 ± 0.94	2.47 ± 1.06	1.81 ± 1.17	2.20 ± 1.01
Unscheduled euthanasia	0	0	0	0
Number of surviving pregnant females	12	14	16	14
Corpora lutea Mean number per liter ± SD	181 15.08 ± 0.67	236 16.08 ± 1.17	248 15.50 ± 1.67	213 15.21 ± 1.97
Implantations Mean number per liter	169 14.08 ± 2.31	221 15.79 ± 0.97	233 14.56 ± 2.25	201 14.36 ± 1.86
Pre-implantation loss Percent to the # of corpora lutea	12 6.63	15 6.36	15 6.05	12 5.63

Dose (mg/kg/day)	0	0.02	0.06	0.18
Live fetuses Percent to the # of corpora lutea	159 13.25 ± 2.56	200 14.29 ± 1.94	209 13.06 ± 2.52	192 13.71 ± 2.02
Dead fetuses Percent to the # of implants	10 5.92	21 9.50	24 11.30	9 4.48

Study title: CMA-676: Intravenous Male Fertility Study in Rats

Study no.:	40369
Study report location:	eCTD 4.2.3.5.1
Conducting laboratory and location:	Safety Assessment Research Medical Research Laboratories Wyeth Lederle Japan, Ltd. Saitama 353-8511 , Japan
Date of study initiation:	September 29, 1999
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	CMA-676; 111196-R2024-2; 5 mg vial Protein content: 4.85 mg, Total calicheamicin derivatives: 29.1 mcg/mg

Key Study Findings

- CMA-676 affected the clonal expansion and maturation of germinal cells in the seminiferous tubules indicated by decreased spermatogonium and spermatocyte in all male rats at all dose levels that mated at the end of dosing. However, the quality and quantity of the sperm of these male rats was not affected during the 4-week dosing. Decrease in sperm and cell debris in the lumen of the epididymides occurred at the highest dose of 0.18 mg/kg/day (1.08 mg/m^2/day) resulting in a small number of impregnated female rats at this dose levels but in general, the reproductive ability was similar to control rats.
- CMA-676-related effects on the clonal expansion and maturation of germinal cells in the seminiferous tubules were less severe in male rats that underwent 9-weeks recovery. However, latest stages of the spermatogenesis cycle were significantly affected alone with pronounced decrease in sperm and cell debris in the lumen of the epididymides resulting in an impaired reproductive ability at ≥0.02 mg/kg/day (0.12 mg/m^2/day) after a 9-week recovery period.

Methods

Doses:	0, 0.02, 0.06, or 0.18 mg/kg/day 0, 0.12, 0.36, or 1.08 mg/m^2/day Dose levels selected based on a DRF in rats
Frequency of dosing:	Daily for 28 days
Dose volume:	1 mL/kg
Route of administration:	IV
Formulation/Vehicle:	Phosphate buffered saline supplemented with 1.0% rat serum albumin and 1.55% sucrose
Species/Strain:	Crj:CD(SD)IGS rats
Number/Sex/Group:	32 males/group
Satellite groups:	None
Study design:	Dosing during pre-mating period only
Deviation from study protocol:	None

Observations

Dose selection: In a preliminary study, decrease in erythrocytes and increase in ALT at 0.12 mg/kg/day and above, decreases in body weight, food consumption, testis weight and numbers of sperm at 0.18 mg/kg/day and above were observed. However, male fertility indices were 100% in all the groups (0.06, 0.12, 0.18 and 0.24 mg/kg/day). Therefore, dosage of 0.18 mg/kg/day that is expected to give toxic effects including testis toxicity was selected as the highest dose level of this study. Dosages of 0.06 and 0.02 mg/kg/day were selected as the intermediate and lowest dose levels, respectively, in a common ratio of 3.

Table 29 Experimental Design Male Fertility Study

(Excerpted from Submission)

Group	Dosage[1)] (mg/kg/day)	Concentration (mg/mL)	Dose volume (mL/kg)	No. of animal		Animal No.
				Total	Recovery	
Control	0	0	1	32	16	801~816, 817~832[2)]
CMA-676	0.02	0.02	1	32	16	833~848, 849~864[2)]
CMA-676	0.06	0.06	1	32	16	865~880, 881~896[2)]
CMA-676	0.18	0.18	1	32	16	897~912, 913~928[2)]

1) Dosage was expressed as the total quantity of the hP67.6 antibody and calicheamicin conjugate. Dosages of the hP67.6 antibody are 0.019, 0.058, and 0.175 mg/kg/day, and dosages of the calichemicin are 0.55, 1.69, and 5.09 μg/kg/day in the 0.02, 0.06, and 0.18 mg/kg groups of CMA-676, respectively. Dosing concentration analyses of the low, middle and high dose groups

Mating: 16 males/group mated with untreated females after 28-day dosing; 16 males/group underwent 9-weeks recovery before mating with untreated females. Cohabitation conducted overnight one-on-one basis for 5 days. Successful copulation was confirmed by the presence of vaginal plug or sperm in the vaginal smear in the next morning, and the day of successful copulation was designated as day 0 of gestation (GD0).

Reproductive ability: precoital interval for successful copulation.
Copulation index (number of copulated animals/number of mated animalsx100)
Male fertility index (number of pregnant females/number of copulated malesx100)

Sperm Examination: right caudal epididymis of all males was weighed on the day of successful copulation, sperm collected from the right caudal epidiymis, and count of sperm and sperm motility were examined under the microscope. Results expressed as count of sperm per gram caudal epididymis and sperm motility (number of motile sperm/number of sperm examinexl00).
Smear preparation of the sperm samples were examined and sperm form anomalies index calculated (number of abnormal sperm/number of sperm examinedxl00).

Necropsy, Organ Weight Measurement and Histopathological Examination:
Males were euthanized on the day of successful copulation. Organ weight measured for the thymus, liver, spleen, kidneys, testes and epididymides. Microscopic examination for the testes and epididymides of the 0.02 and 0.06 mg/kg groups was conducted since changes were observed in the testes and epididymides of the 0.18 mg/kg/day.

Hysterectomy: conducted on GD14 for females with successful copulation.
Numbers of corpora lutea, implants, and dead and live embryos were counted
Pre-implant loss index [(number of corpora lutea - number of implants) /number of corpora lutea]
Dead embryo index (number of dead embryos/number of implantsx100)

Results

Mortality

None

Clinical Signs

Unremarkable

Body Weight

No CMA-676-related effects in mean body weight or body weight gain during dosing or recovery period.

Food Consumption

No CMA-676-related effects in food consumption.

Toxicokinetics

Toxicokinetics in male rats was evaluated in study MIRACL-26813 “Six-Cycle Intravenous Toxicity of hP67.6 in Rats followed by a Four-week Recovery Period” The lowest dose of hP67.6 (0.1 mg/kg) used in the repeat-dose study was approximately 1.6 times the dose used in the male fertility study (0.06 mg/kg/day). TK parameters could not be calculated at the end of the dosing period for females. Therefore, the combined gender mean $AUC_{(0\text{-}168)}$ of 90.6 mcg*h/mL calculated after the first day of dosing at the

lowest dose of 0.1 mg/kg was chosen to estimate animal to human exposure ratios in section 8 of the prescribing information.

Table 30 Toxicokinetics of hP67.6 in Rats

(Excerpted from Submission)

Group	Sex	Day	Dose (mg/kg)	Cmax (µg/mL)	Tmax (hr)	AUC(0-168) (µg.hr/mL)	AUC(0-inf) (µg.hr/mL)	t1/2 (hr)	CLT (mL/hr/kg)	Vss (L/kg)
6	Male	0	1.2	25.7	IAD	1370	1740	83	0.69	0.08
	Female	0	1.2	30.5	IAD	1220	1620	92	0.74	0.09
	Both	0	1.2	28.1	IAD	1300	1680	87	0.71	0.08
	Male	35	1.2	26.0	IAD	1580	1800	54	0.67	0.05
	Female	35	1.2	34.6	IAD	2490	2820	54	0.43	0.03
	Both	35	1.2	30.3	IAD	2080	2460	63	0.49	0.04
7	Male	0	0.1	2.09	IAD	101	116	56	0.86	0.07
	Female	0	0.1	1.59	IAD	79.0	97.1	79	1.03	0.11
	Both	0	0.1	1.84	IAD	90.6	106	65	0.94	0.08
	Male	35	0.1	4.38	2	335	514	136	0.19	0.04
	Female	35	0.1	1.26	2	ND	ND	ND	ND	ND
	Both	35	0.1	2.82	2	ND	ND	ND	ND	ND
8	Male	0	0.4	8.25	IAD	433	561	85	0.71	0.08
	Female	0	0.4	7.99	2	371	561	122	0.71	0.11
	Both	0	0.4	7.89	2	403	555	99	0.72	0.09
	Male	35	0.4	6.13	2	ND	ND	ND	ND	ND
	Female	35	0.4	0.41	IAD	ND	ND	ND	ND	ND
	Both	35	0.4	1.15	IAD	ND	ND	ND	ND	ND
9	Male	0	1.2	34.9	IAD	1240	1500	74	0.80	0.07
	Female	0	1.2	28.4	IAD	1120	1330	70	0.90	0.08
	Both	0	1.2	31.7	IAD	1180	1420	72	0.85	0.08
	Male	35	1.2	12.5	2	ND	ND	ND	ND	ND
	Female	35	1.2	3.47	2	ND	ND	ND	ND	ND
	Both	35	1.2	7.97	2	ND	ND	ND	ND	ND

ND Not determined. IAD Immediately after dose.

Dosing Solution Analysis

CMA-676 is a white powder, and has been confirmed to be stable for (b) (4) month in a refrigerator under the dark. CMA-676 dosing solution was prepared immediately before use. The concentrations of CMA-676 in mixture were measured at the first and final preparations and the concentrations were within acceptable limits (variation within ±25%), see Table 31.

Table 31 CMA-676 Formulation Analysis in the Male Fertility Study

(Excerpted from Submission)

First Preparation

Nominal CMA-676 concentration(mg/mL)	Nominal protein concentration(mg/mL)	Measured protein concentration(mg/mL)	Percentage to nominal protein Concentration (%)
0.02	0.01944	0.01992	102.5
0.06	0.05832	0.05872	100.7
0.18	0.17496	0.16672	95.3

Last Preparation

Nominal CMA-676 concentration(mg/mL)	Nominal protein concentration(mg/mL)	Measured protein concentration(mg/mL)	Percentage to nominal protein Concentration (%)
0.02	0.01944	0.01884	96.9
0.06	0.05832	0.05568	95.5
0.18	0.17496	0.15424	88.2

Male Reproductive Ability

In males that mated at the end of the dosing period, no CMA-676-related effects occurred in male fertility indices except for a decreased number of female rats pregnant at 0.18 mg/kg/day.

Table 32 Reproductive Ability of Male Rats that Mated at the end of Dosing

Dose (mg/kg/day)	0	0.02	0.06	0.18
Number of males / females tested	16 / 16	16 / 16	16 / 16	16 / 16
Number of copulated males / females	16 / 16	16 / 16	16 / 16	16 / 16
Number of females pregnant	15 (93.8)	15 (93.8)	16 (100)	13 (81.3)
Duration of mating (mean days ± SD)	2.31 ± 1.49	1.88 ± 0.81	1.69 ± 0.95	2.25 ± 1.06

In males that mated at the end of the recovery period, CMA-676 significantly affected the ability of male rats to impregnate females at all doses tested.

Table 33 Reproductive Ability of Male Rats that Mated at the end of 9-week Recovery

Dose (mg/kg/day)	0	0.02	0.06	0.18
Number of males / females tested	16 / 16	16 / 16	16 / 16	16 / 16
Number of copulated males / females	16 / 16	16 / 16	16 / 16	16 / 16
Number of females pregnant	16 (100)	4 (25.0)	0 (0)	1 (6.3)
Duration of mating (mean days ± SD)	2.81 ± 0.83	2.75 ± 1.24	2.50 ± 1.21	2.94 ± 0.57

Sperm Analysis

In males that mated at the end of the dosing period, no significant CMA-676-related effects occurred in sperm analysis parameters. A decrease in sperm counts, motility and an increase in the anomalies index occurred at 0.18 mg/kg/day.

Table 34 Sperm Analysis Parameters of Male Rats Mated at the End of Dosing

(Excerpted from Submission)

Group and dose	Control	0.02 mg/kg	0.06 mg/kg	0.18 mg/kg
No. of examined	16	16	16	16
Count of sperm(×10⁶ /g)	328.81±114.28	329.20± 71.05	264.14± 80.25	150.48±131.35
Sperm motility(%)	97.48± 2.13	96.38± 1.98	95.84± 2.79	89.25± 20.89
Sperm form anomalies index(%)	1.08± 0.56	1.06± 0.49	0.98± 0.59	2.07± 1.02 a)

Not significantly different from control.
Values are mean±S.D.
a) n=15

In males that mated at the end of the recovery period, CMA-676 significantly affected the quality and quantity of sperm in a dose-related manner (Table 35) that corresponded with the CMA-676-related impaired reproductive ability as shown in Table 33.

Table 35 Sperm Analysis Parameters of Male Rats Mated at the end of 9-week Recovery

(Excerpted from Submission)

Group and dose	Control	0.02 mg/kg	0.06 mg/kg	0.18 mg/kg
No. of examined	16	16	16	16
Count of sperm(×10⁶ /g)	404.78± 76.52	69.89±119.75**	51.71± 71.93	27.02± 35.16
Sperm motility(%)	98.53± 1.33	34.61± 40.25	6.69± 24.44	0.14± 0.27
Sperm form anomalies index(%)	1.52± 0.98	35.13± 36.18 a)	82.88± 26.12 b)	88.60± 17.66 b)

**: P<0.01 (significantly different from control).
Values are mean±S.D.
a) n=13
b) n=14

Hysterectomy Evaluations of Untreated Females

No significant differences occurred in hysterectomy parameters of untreated females mated with CMA-676-treated male rats at the end of dosing. The number of corpora lutea, implantations and live fetuses were decreased at 0.18 mg/kg/day. These results correspond with findings in male reproductive ability and sperm analysis at the same CMA-676 dose of 0.18 mg/kg/day that included a decrease in number of females pregnant, sperm counts, motility and an increase in sperm form anomalies index.

Table 36 Hysterectomy Parameters of Untreated Female Rats Mated with CMA-676 Treated Males at the end of Dosing

Dose (mg/kg/day)	0	0.02	0.06	0.18
Number of females pregnant	15	15	16	13
Corpora lutea Mean number per liter ± SD	235 15.67 ± 1.45	219 14.60 ± 1.40	239 14.94 ± 1.12	195 15.00 ± 2.12

Dose (mg/kg/day)	0	0.02	0.06	0.18
Implantations Mean number per liter	227 15.13 ± 1.06	211 14.07 ± 2.05	236 14.75 ± 1.34	189 14.54 ± 2.70
Pre-implantation loss Percent to the # of corpora lutea	8 3.40	8 3.65	3 1.26	6 3.08
Live fetuses Percent to the # of corpora lutea	216 14.40 ± 1.30	199 13.27 ± 1.91	214 13.38 ± 1.45	171 13.15 ± 3.05
Dead fetuses Percent to the # of implants	11 4.85	127 5.69	22 9.32	18 9.52

In untreated females that mated with CMA-676-treated male rats at the end of the recovery period, CMA-676 significantly affected all hysterectomy parameters.

Table 37 Hysterectomy Parameters of Untreated Female Rats Mated with CMA-676 Treated Males at the end of 9-week Recovery

Dose (mg/kg/day)	0	0.02	0.06	0.18
Number of females pregnant	16	4	0	1
Corpora lutea Mean number per liter ± SD	249 15.56 ± 1.97	55 13.75 ± 1.71		2 2.00 ± --
Implantations Mean number per liter	238 14.88 ± 1.20	48 12.00 ± 2.00		1 1.00 ± --
Pre-implantation loss Percent to the # of corpora lutea	11 4.42	7 12.73		1 50.00
Live fetuses Percent to the # of corpora lutea	227 14.19 ± 1.56	44 11.00 ± 2.16		0
Dead fetuses Percent to the # of implants	11 4.62	4 8.33		1 100

Necropsy

In males that mated at the end of the dosing period, small testis and epididymis were observed at ≥0.06 mg/kg/day, see Table 38. Macroscopic observations corresponded with dose-related decreased testis-to-body weight ratios, see Table 40. Similar macroscopic findings occurred in a dose-related manner at ≥0.02 mg/kg/day in males that mated at the end of the recovery period, see Table 39, with corresponding dose-related decreased absolute and relative testis weight, see Table 41.

Table 38 Macroscopic Findings for Male Rats that Mated at the end of Dosing

(Excerpted from Submission)

Sex	Male			
Group and dose	Control	0.02 mg/kg	0.06 mg/kg	0.18 mg/kg
Organs and findings / Number of animals	16	16	16	16
Urinary system				
Kidney				
Dilatation, pelvic cavity	0	0	1	0
Genital system				
Testis				
Small	0	0	1	10
Epididymis				
Small	0	0	1	5

No appreciable changes in all other organs and tissues.

Table 39 Macroscopic Findings for Male Rats that Mated at the end of 9-week Recovery

(Excerpted from Submission)

Sex	Male			
Group and dose	Control	0.02 mg/kg	0.06 mg/kg	0.18 mg/kg
Organs and findings / Number of animals	16	16	16	16
Genital system				
Testis				
Small	0	4	13	15
Epididymis				
Small	0	7	12	10

No appreciable changes in all other organs and tissues.

Table 40 Absolute and Relative Organ Weight of Male Rats that Mated at the end of Dosing

(Excerpted from Submission)

Group and dose	Control	0.02 mg/kg	0.06 mg/kg	0.18 mg/kg
No. of animals	16	16	16	16
Absolute organ weights				
Final body weight (g)	399.0±26.9	395.8±28.6	370.5±30.0	334.2±23.8
Thymus (g)	0.34±0.10	0.35±0.09	0.32±0.07	0.23±0.06
Liver (g)	13.30±1.76	14.15±1.42	13.60±1.74	12.93±1.86
Spleen (g)	0.73±0.11	0.75±0.07	0.72±0.12	0.64±0.10
Kidneys (g)	2.76±0.25	2.73±0.23	2.64±0.22	2.44±0.24
Epididymides (g)	0.96±0.09	0.99±0.05	0.93±0.10	0.70±0.11
Testes (g)	3.17±0.27	2.82±0.17	2.48±0.26	1.68±0.47
Relative organ weights				
Thymus (g/100gB.W.)	0.09±0.02	0.09±0.02	0.09±0.02	0.07±0.02
Liver (g/100gB.W.)	3.33±0.34	3.58±0.27	3.66±0.27	3.86±0.42
Spleen (g/100gB.W.)	0.18±0.03	0.19±0.02	0.19±0.02	0.19±0.03
Kidneys (g/100gB.W.)	0.69±0.04	0.69±0.05	0.71±0.06	0.73±0.05
Epididymides (g/100gB.W.)	0.24±0.03	0.25±0.02	0.25±0.04	0.21±0.03
Testes (g/100gB.W.)	0.80±0.08	0.72±0.06	0.67±0.09	0.50±0.13

Table 41 Absolute and Relative Organ Weight of Male Rats that Mated at the end of 9-week Recovery

(Excerpted from Submission)

Group and dose	Control	0.02 mg/kg	0.06 mg/kg	0.18 mg/kg
No. of animals	16	16	16	16
Absolute organ weights				
Final body weight (g)	553.0±43.7	535.0±51.8	515.2±44.9	505.4±33.9
Thymus (g)	0.22±0.06	0.25±0.07	0.26±0.06	0.23±0.06
Liver (g)	17.12±1.66	17.51±2.05	16.13±1.93	15.75±2.62
Spleen (g)	0.84±0.11	0.84±0.11	0.86±0.11	0.90±0.16
Kidneys (g)	3.25±0.26	3.15±0.28	3.17±0.32	3.16±0.32
Epididymides (g)	1.18±0.06	0.85±0.15	0.78±0.09	0.75±0.09
Testes (g)	3.33±0.32	2.43±0.64	1.50±0.51	1.30±0.34
Relative organ weights				
Thymus (g/100gB.W.)	0.04±0.01	0.05±0.01	0.05±0.01	0.05±0.01
Liver (g/100gB.W.)	3.10±0.18	3.28±0.28	3.13±0.18	3.10±0.37
Spleen (g/100gB.W.)	0.15±0.02	0.16±0.02	0.17±0.02	0.18±0.03
Kidneys (g/100gB.W.)	0.59±0.04	0.59±0.04	0.62±0.04	0.63±0.05
Epididymides (g/100gB.W.)	0.21±0.01	0.16±0.02	0.15±0.02	0.15±0.02
Testes (g/100gB.W.)	0.60±0.06	0.45±0.11	0.29±0.10	0.26±0.07

Histological Findings

Table 42 Microscopic Findings in CMA-676-treated Male Rats that Mated at the end of Dosing

(Excerpted from Submission)

Organs and findings \ Sex	Male																			
Group and dose	Control					0.02 mg/kg					0.06 mg/kg					0.18 mg/kg				
Number of animals	16					16					16					16				
	−	+	++	+++	Total	−	+	++	+++	Total	−	+	++	+++	Total	−	+	++	+++	Total
Genital system																				
Testis			(16)					(16)					(16)					(16)		
Decrease, spermatogonium	16	0	0	0	0	0	0	15	1	16	0	0	0	16	16	0	0	0	16	16
Decrease, spermatocyte	16	0	0	0	0	0	16	0	0	16	0	0	15	1	16	0	0	5	11	16
Decrease, spermatid (round)	16	0	0	0	0	16	0	0	0	0	15	0	1	0	1	5	3	0	8	11
Decrease, spermatid (elongate)	16	0	0	0	0	16	0	0	0	0	15	0	0	1	1	5	3	0	8	11
Vacuolation, nucleus, spermatid (round)	16	0	0	0	0	16	0	0	0	0	16	0	0	0	0	9	6	1	0	7
Appearance, giant cell	16	0	0	0	0	16	0	0	0	0	16	0	0	0	0	6	9	1	0	10
Epididymis			(16)					(16)					(16)					(16)		
Decrease, sperm	16	0	0	0	0	16	0	0	0	0	15	0	0	1	1	9	2	2	3	7
Debris, cell, lumen	16	0	0	0	0	16	0	0	0	0	15	1	0	0	1	8	8	0	0	8
Granuloma, spermatic	15	1	0	0	1	15	1	0	0	1	16	0	0	0	0	16	0	0	0	0

Grade sign: −, none; +, slight; ++, moderate; +++, severe.
Figures in parentheses are number of animals with tissues examined histopathologically.

Table 43 Microscopic Findings in CMA-676-treated Male Rats that Mated at the end of 9-week Recovery

(Excerpted from Submission)

Organs and findings \ Sex	Male																			
Group and dose	Control					0.02 mg/kg					0.06 mg/kg					0.18 mg/kg				
Number of animals	16					16					16					16				
	−	+	++	+++	Total	−	+	++	+++	Total	−	+	++	+++	Total	−	+	++	+++	Total
Genital system																				
Testis			(16)					(16)					(16)					(16)		
Decrease, spermatogonium	16	0	0	0	0	15	0	0	1	1	4	4	1	7	12	1	4	0	11	15
Decrease, spermatocyte	16	0	0	0	0	14	1	0	1	2	3	2	3	8	13	0	1	4	11	16
Decrease, spermatid (round)	16	0	0	0	0	10	5	0	1	6	1	4	2	9	15	0	1	3	12	16
Decrease, spermatid (elongate)	16	0	0	0	0	7	5	3	1	9	1	2	0	13	15	0	1	3	12	16
Appearance, giant cell	16	0	0	0	0	16	0	0	0	0	14	2	0	0	2	16	0	0	0	0
Epididymis			(16)					(16)					(16)					(16)		
Decrease, sperm	16	0	0	0	0	2	1	4	9	14	1	0	12	3	15	0	0	9	7	16
Debris, cell, lumen	16	0	0	0	0	8	6	2	0	8	3	12	1	0	13	4	12	0	0	12
Granuloma, spermatic	16	0	0	0	0	15	1	0	0	1	16	0	0	0	0	16	0	0	0	0

Grade sign: −, none; +, slight; ++, moderate; +++, severe.
Figures in parentheses are number of animals with tissues examined histopathologically.

9.2 Embryonic Fetal Development

The following studies were previously reviewed. A summary of findings is included.

Study No. 33248: CMA-676 (With Rat Serum Albumin): Intravenous Developmental Toxicity Dose Ranging Study in Gravid Rats.

Summary of Findings

Daily maternal treatment of rats during the period of organogenesis from GD 6 to GD 17 with CMA-676 at 0, 0.025, 0.075 or 0.2 mg/kg/day (0, 0.15, 0.45 or 1.2 mg/m^2) produced dose-related decreases in fetal weights at the doses of 0.025 and 0.075 mg/kg/day, dose-related increases in embryofetal mortality at 0.075 and 0.2 mg/kg/day, and fetal digital malformations at the dose of 0.075 mg/kg/day. At the dose of 0.2 mg/kg, the resorption of all implantations precluded fetal evaluations.

Table 44 CMA-676-related Effects on Rat Maternal Body Weights and Food Consumption - DRF

(Excerpted from Review)

	0.025 mg/kg	0.075 mg/kg	0.2 mg/kg
Maternal body wt. gain (GD 6 – 17)	↓ 16 %	↓ 60 %	*
Maternal body wt. gain (GD 18 – 20)	↓ 12 %	↓ 74 %	*
Gravid uterine wt.	↓ 11 %	↓ 79 %	↓ 98 %
Maternal body wt. (GD 21)	↓ 4 %	↓ 22 %	↓ 36 %
Maternal food consumption values	↓ 4 %	↓ 17 %	↓ 28 %
Maternal food consumption values (during post-dosing period)		↓ 9 %	↓ 41 %

*No body wt. gain. Loss of 5.4 g during GD 6 – 17 and loss of 3.9 g during GD 18 – 20.

Table 45 CMA-676-related Hysterectomy Findings - DRF

(Excerpted from Review)

Hysterotomy findings: The mean number of corpora lutea and implantations per dam were comparable among all groups

	Control	0.025 mg/kg	0.075 mg/kg	0.20 mg/kg
Embryo/fetal mortality				
Early resorptions per litter	1.13	0.75	10.13	13.38
Late resorptions per litter	0	0	0.13	
Average # of live fetuses per litter	10.88	11.13	2.88	0

Study No. 33829: CMA-676: Intravenous Developmental Toxicity Study in Gravid Rats.

Summary of Findings

Daily maternal treatment of rats during the period of organogenesis from GD 6 to GD 17 with CMA-676 at 0, 0.010, 0.025, or 0.060 mg/kg/day (0, 0.06, 0.15, or 0.36 mg/m^2) produced increased embryofetal mortality, decreased numbers of live fetuses per litter, and low fetal incidences of gross external, visceral and skeletal anomalies. At the dose of 0.025 mg/kg/day, fetal skeletal anomalies were present in a single fetus. In the 0.010 mg/kg/day group, only a slight decrease in skeletal ossification was observed. Effects on fetal weight, ossification, and wavy ribs became apparent at 0.025 mg/kg/day.

Table 46 CMA-676-related Effects on Rat Maternal Body Weights and Food Consumption

(Excerpted from Review)

	0.010 mg/kg	0.025 mg/kg	0.060 mg/kg
Maternal body wt. gain (GD 6 – 17)	↓ 7 %	↓ 15 %	↓ 43 %
Maternal body wt. gain (GD 18 – 20)	↓ 8 %	↓ 19 %	↓ 56 %
Gravid uterine wt.	↓ 7 %	↓ 17 %	↓ 59 %
Maternal adjusted pregnancy wt. gain (GD 6 – 20)	↓ 7 %	↓ 18 %	↓ 23 %
Maternal food consumption values	↓ 4 %	↓ 4 %	↓ 11 %
Maternal food consumption values (during post-dosing period)		↓ 5 %	↓ 8 %

Table 47 CMA-676-related Hysterectomy Findings

(Excerpted from Review)

Hysterotomy findings:	Control	0.010 mg/kg	0.025 mg/kg	0.060 mg/kg
Embryo/fetal mortality				
Early resorptions per litter	0.79	0.42	0.50	4.17
Early resorptions proportion/litter	0.06	0.03	0.05	0.35
Late resorptions per litter	0	0	0	0.46
Late resorptions proportion/litter	0	0	0	0.04
Average # of live fetuses per litter	12	11.75	11.42	7.46
Live fetuses proportion/litter	0.94	0.97	0.95	0.61

No drug-related effect on total implantations, preimplantation loss, and corpora lutea.

9.3 Prenatal and Postnatal Development

Not conducted

10 Appendix/Attachments

List of Studies submitted to the BLA. Studies highlighted in yellow were reviewed. Others were previously reviewed under NDA 21174 or not reviewed at all.

Application: 761060


4.2.3. Toxicology
4.2.3.1. Single-Dose Toxicity [Species - Route of Administration]
4.2.3.1. Mouse - Intravenous [Study ID - Study Title]
4.2.3.1. rpt-77183 - Single Dose (Intravenous) Toxicity Study in Mice
4.2.3.1. Nonhuman Primate - Intravenous [Study ID - Study Title]
4.2.3.1. miracl-26710 - A Single Dose Intravenous Toxicity Study of CL 555,201 (N-Acetyl-Gamma-Dimethyl-Hydrazide-Acetyl-Butyryloxy Derivative of Calicheamicir
4.2.3.1. miracl-26817 - An Exploratory Single Dose Intravenous Tolerance Study of CL 555,201 (N-Acetyl-Gamma-Dimethyl-Hydrazide-Acetyl-Butyryloxy Derivative
4.2.3.1. Rat - Intravenous [Study ID - Study Title]
4.2.3.1. miracl-26631 - A Single Dose Intravenous Toxicity Study of CL 555,201 (N-Acetyl-Gamma-Dimethyl-Hydrazide-Acetyl-Butyryloxy Derivative of Calicheamicir
4.2.3.1. miracl-26711 - An Exploratory Single Dose Intravenous Tolerance Study of CL 555,201 (N-Acetyl-Gamma-Dimethyl-Hydrazide-Acetyl-Butyryloxy Derivative
4.2.3.2. Repeat-Dose Toxicity (including supportive toxicokinetics evaluations) [Species - Route of Administration - Duration]
4.2.3.2. Nonhuman Primate - Intravenous - Short [Study ID - Study Title]
4.2.3.2. gtr-27677 - Six Cycle Intravenous Comparative Toxicity Study in Male Monkeys
4.2.3.2. miracl-26812 - A Six Cycle Intravenous Toxicity Study of CL 555,201 (N-Acetyl-Gamma-Dimethyl-Hydrazide-Acetyl-Butyryloxy Derivative of Calicheamicin [C
4.2.3.2. Rabbit - Intravenous - Short [Study ID - Study Title]
4.2.3.2. gtr-33261 - CMA-676 (with Rabbit Serum Albumin) Multiple Dose (13 Day) Intravenous Tolerablity Study in Female (Non-Gravid) Rabbits with Two-Week P
4.2.3.2. Rat - Intravenous - Short [Study ID - Study Title]
4.2.3.2. miracl-26813 - Six Cycle Intravenous Toxicity Study of CL 555,201 (N-AcetylGamma-Dimethyl-Hydrazide-Acetyl-Butyryloxy Derivative ofCalicheamicin [CL 1
4.2.3.3. Genotoxicity
4.2.3.3.2. In vivo (including supportive toxicokinetics evaluations) [Study ID - Study Title]
4.2.3.3.2 gtr-28070 - Mutagenicity Test On CMA-676/Calicheamicin in an In Vivo Mouse Micronucleus Assay
4.2.3.5. Reproductive and Developmental Toxicity (including range-finding studies and supportive toxicokinetics evaluations) (If modified study designs are used, the follow
4.2.3.5.1. Fertility and early embryonic development [Study ID - Study Title]
4.2.3.5.1. 39279 - Intravenous Female Fertility Dose Ranging Study in Rats
4.2.3.5.1. 39635 - Intravenous Male Fertility Dose Ranging Study in Rats
4.2.3.5.1. 40230 - Intravenous Female Fertility Study in Rats
4.2.3.5.1. 40369 - Intravenous Male Fertility Study in Rats
4.2.3.5.2. Embryo-fetal development [Study ID - Study Title]
4.2.3.5.2. gtr-33248-34359 - CMA-676 with Rat Serum Albumin Intravenous Developmental Toxicity Dose Ranging Study in Gravid Rats
4.2.3.5.2. gtr-33829 - Intravenous Developmental Toxicity Study in Gravid Rats
4.2.3.7. Other Toxicity Studies (if available)
4.2.3.7.7. Other [Study ID - Study Title]
4.2.3.7.7. 14gr346 - 9-Week Intravenous Bolus Investigative Toxicity Study of PF-06647259 in Cynomolgus Monkeys
4.2.3.7.7. 15gr142 - In Vitro Micronucleus Assay in TK6 Cells
4.2.3.7.7. 15gr143 - Salmonella-E. Coli/Mammalian Microsome Reverse Mutation Assay
4.2.3.7.7. 16gr009 - Neutral Red Uptake Phototoxicity Assay of PF-06649266 in BALB/c 3T3 Mouse Fibroblasts
4.2.3.7.7. gtr-35397 - Reactivity of Humanized P67 Antibody (CDP771) to Normal Human Tissues
4.2.3.7.7. gtr-35398 - Reactivity of Humanized P67.6 Conjugate (CDP771/CL 555,201) To a Panel of Normal Human Tissues
4.2.3.7.7. gtr-35399 - Reactivity of Humanized P67.6 Antibody (CDP771/CL 555,001) To a Panel of Normal Human Tissue
4.2.3.7.7. gtr-35400 - Reactivity of Humanized P67.6 and hP67.6-Calicheamicin Conjugate (CDP771/2) to a Panel of Normal Human Tissues. Equivalence Study f
4.2.3.7.7. miracl-24627 - A Single Intravenous Dose Exploratory Study of Calicheamicin (CAL) Analogs (Antitumor Antibiotics) in Mice
4.2.3.7.7. miracl-25706 - A Single Dose Intravenous Toxicity Study of CL 190,396 (N-Acetyl-Epsilon Derivative of Calicheamicin), an Anticancer Agent, in Rats
4.2.3.7.7. miracl-25707 - A Single Dose Intravenous Toxicity Study of CL 190,396 (N-Acetyl-Epsilon Derivative of Calicheamicin), an Anticancer Agent, in Dogs
4.2.3.7.7. miracl-26628 - A Single Dose Intravenous Toxicity Study of CL 184,538 (N-Acetyl-Gamma-Dimethyl-Hydrazide Derivative of Calicheamicin), an Anticance
4.2.3.7.7. miracl-26629 - A Single Dose Intravenous Toxicity Study of CL 184,538 (N-Acetyl-Gamma-Dimethyl-Hydrazide Derivative of Calicheamicin), an Anticance
4.2.3.7.7. miracl-26630 - A Six Week Intravenous Toxicity Study of CL 184,538 (N-Acetyl-Gamma-Dimethyl-Hydrazide Derivative of Calicheamicin), an Anticancer A
4.2.3.7.7. miracl-26707 - A Six Week Intravenous Toxicity Study of CL 184,538 (N-Acetyl-Gamma-Dimethyl-Hydrazide Derivative of Calicheamicin), an Anticancer A
4.2.3.7.7. miracl-26709 - A Single Dose Intravenous Toxicity Study of CL 191,305 (N-Acetyl-Gamma-Dimethyl-Hydrazide-AcBut Derivative of Calicheamicin), an Ant
4.2.3.7.7. miracl-26808 - Cross Reactivity of Humanized Monoclonal Antibody hP67.6 with Tissues of Cynomolgus Monkeys and Sprague-Dawley Rats
4.2.3.7.7. miracl-26816 - In Vitro Blood Compatibility of CL 555,201 (N-Acetyl-Gamma-Dimethyl-Hydrazide-Acetyl-Butyryloxy Derivative of Calicheamicin [CL 191,305
4.3. Literature References
5. Clinical Study Reports

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/s/

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07/31/2017

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