CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761121Orig1s000

NON-CLINICAL REVIEW(S)

MEMORANDUM

Date: May 23, 2019

From: Haleh Saber, PhD
Deputy Director, Division of Hematology Oncology Toxicology (DHOT)
Office of Hematology and Oncology Products (OHOP)
CDER/ FDA

To: File for BLA 761121

Product: POLIVY (polatuzumab vedotin)

I have examined pharmacology/ toxicology review conducted by Dr. Gudi and Dr. Simpson and secondary memorandum provided by Dr. Christopher Sheth. I concur with Dr. Sheth's conclusion that from a nonclinical perspective, POLIVY may be approved for the proposed indication of relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and that no additional nonclinical studies are needed for this indication. The labeling negotiation is currently ongoing.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

HALEH SABER
05/23/2019 02:30:24 PM

MEMORANDUM

Date: May 23, 2019
From: Christopher Sheth, PhD
Division of Hematology Oncology Toxicology (DHOT)
Office of Hematology and Oncology Products (OHOP)
Re: Approvability for Pharmacology and Toxicology
BLA: 761121
Drug: Polivy (polatuzumab vedotin)
Indication: Relapsed or refractory diffuse large B-cell lymphoma (DLBCL)
Applicant: Roche/Genentech

Polatuzumab vedotin is a CD79b-directed antibody-drug conjugate consisting of the anti-mitotic agent monomethyl auristatin E (MMAE) linked to a humanized IgG1 antibody for the treatment of patients with diffuse large B-cell lymphoma (DLBCL). Dr. Ramadevi Gudi and Dr. Natalie Simpson reviewed the pharmacology and toxicology studies submitted in support of the BLA. The BLA contains an appropriate complement of nonclinical studies characterizing the primary pharmacodynamics, genotoxicity, safety pharmacology, repeat dose toxicology, and embryo-fetal developmental toxicity of polatuzumab vedotin. The nonclinical findings are summarized in the "Executive Summary" of the BLA review and reflected in the product label. I concur with the pharmacology/toxicology reviewers that from a nonclinical perspective, Polivy may be approved and that no additional nonclinical studies are needed to support approval of Polivy for DLBCL.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CHRISTOPHER M SHETH
05/23/2019 10:25:10 AM

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:	BLA 761121
Supporting document/s:	0002
Applicant's letter date:	December 21, 2018
CDER stamp date:	December 19, 2018
Product:	POLIVY (polatuzumab vedotin)
Indication:	Relapsed or refractory diffuse large B-cell lymphoma (DLBCL)
Applicant:	Roche/Genentech
Review Division:	Division of Hematology Oncology Toxicology (DHOT) for Division of Hematology Products (DHP)
Reviewers:	Ramadevi Gudi, PhD
	Natalie E Simpson, PhD
Supervisor/Team Leader:	Christopher M Sheth, PhD
Division Director:	John Leighton, PhD, DABT (DHOT)
	Ann Farrell, MD (DHP)
Project Manager:	Wanda Nguyen

TABLE OF CONTENTS

Table of Tables

Table of Figures

1 Executive Summary

1.1 Introduction

Polatuzumab vedotin is an antibody-drug conjugate (ADC) that consists of the anti-mitotic agent (monomethyl auristatin E [MMAE]) covalently conjugated to a CD79b-directed humanized immunoglobulin (Ig) G1 monoclonal antibody through a protease-cleavable linker, maleimidocaproyl-valine-citrulline-p-aminobenzyloxycarbonyl (mc-vc-PAB) with a drug-to-antibody ratio (DAR) of 3.5. The established pharmacological class will be a CD79b-directed antibody-drug conjugate. CD79b is a signaling component of the B-cell receptor (BCR) and is located on the surface of B-cells, including normal and malignant B-cells (e.g., diffuse large B-cell lymphoma (DLBCL)). The proposed clinical dose of 1.8 mg/kg is to be administered as an intravenous infusion over 90 minutes every 21-days for 6 cycles. Nonclinical pharmacology, pharmacokinetic, and toxicology studies have been submitted to support the approval of polatuzumab vedotin for the treatment of patients with relapsed or refractory DLBCL.

1.2 Brief Discussion of Nonclinical Findings

Polatuzumab vedotin binds to human CD79b, is internalized, cleaved by lysosomal proteases, thereby delivering MMAE to malignant B-cells. The released MMAE binds to microtubules and kills dividing cells by inhibiting cell division and inducing apoptosis. Polatuzumab does not bind to its target epitope on species typically used in toxicology studies. Both polatuzumab vedotin and a surrogate ADC that binds monkey CD79b were used in the toxicology studies. The surrogate ADC carries a targeted average DAR of 3.5. The binding of polatuzumab vedotin to human CD79b-expressing cells, and of the surrogate ADC to monkey CD79b-expressing cells, was characterized with Kds of 1.83 and 1.51 nM, respectively. Polatuzumab vedotin and the surrogate ADC bound FcγIA comparably (~ 10 ng/mL or nM), but polatuzumab vedotin binding was 2- to 3-fold lower than the surrogate ADC and the positive control (rituximab) for other Fcγ receptors (IIA allotypes R131 and H131, IIB, or IIIA allotypes F158 and V158).

In cell-based assays, polatuzumab vedotin antibody-dependent cell-mediated cytotoxicity (ADCC) was one order of magnitude lower than the positive control (rituximab) and no complement-dependent cytotoxicity (CDC) was observed. Polatuzumab vedotin demonstrated anti-tumor activity in vitro in CD79b expressing human Burkitt lymphoma (Ramos) cells (IC_{50} = 0.071 nM) and in vivo in DLBCL and human B-cell lymphoma mouse xenograft models. A single IV dose of 12 mg/kg induced durable complete responses (i.e., no measurable tumor) in 75% of mice in a DLBCL xenograft model. The addition of obinutuzumab or rituximab and bendamustine or CHP [cyclophosphamide (C), doxorubicin (H), prednisone (P)] chemotherapy to 2 mg/kg polatuzumab vedotin reduced the time to tumor doubling.

Safety pharmacology assessments (neurobehavioral, cardiovascular, and respiratory) that were incorporated into the repeat-dose toxicology studies showed no polatuzumab vedotin- or surrogate ADC-induced adverse effects in monkeys. MMAE alone did not

appreciably inhibit the human ether-à-go-go-related gene (hERG) channel (IC50 > 100 µM) in voltage-clamped human embryonic kidney cells.

In an in vitro stability study in human and animal plasma, total antibody concentrations for polatuzumab decreased by 25% over 96 hours at 37^{o}C. The relative stability of polatuzumab vedotin and the surrogate ADC were further confirmed in toxicology studies through pharmacokinetic (PK) data. Studies showed the PK of polatuzumab vedotin and the surrogate ADC were generally comparable. An in vivo pharmacokinetic (PK) study in the same mouse species as the xenograft studies demonstrated that polatuzumab vedotin had a short distribution phase and a long elimination phase, as expected for a monoclonal antibody-based therapeutic. The C_{max} and AUC for a 5 mg/kg dose was approximately 100 µg/mL and 1000 day*µg/mL, respectively, with a half-life of 12 days. In a distribution study in femoral vein-cannulated female Sprague-Dawley rats, polatuzumab vedotin localized in a non-specific manner to multiple highly perfused tissues, including liver, lungs, heart, kidneys, spleen, adrenal gland, ovaries, and bone marrow, with levels peaking 2 hours post-dose. Polatuzumab vedotin underwent catabolism in these tissues, and in a designated excretion study in bile duct cannulated female Sprague-Dawley rats, the major catabolites of polatuzumab vedotin were unconjugated MMAE, O-demethylated MMAE, and amide hydrolysis and N-demethylation with hydroxylation. In a combined distribution and elimination study, MMAE and MMAE-related catabolites of polatuzumab vedotin were primarily eliminated through the hepatobiliary pathway in rats: >95% in feces, ~5% in urine.

MMAE is known to be an in vitro substrate for CYP3A4/5 and P-gp and is not extensively metabolized in vitro or in vivo. In vitro data suggest a low potential for MMAE to result in clinically significant drug-drug interactions (DDIs) with other medications as a perpetrator.

In the repeat-dose rat study, polatuzumab vedotin was administered by intravenous (IV) injection once weekly for 4 weeks at doses of 2, 6, and 10 mg/kg. The adverse effects were observed at all dose levels and included bone marrow hypocellularity with associated hematology effects and liver toxicity, including increased apoptosis/mitoses of hepatocytes, multifocal hepatic necrosis with higher serum liver transaminases, and total bilirubin. Male reproductive organ toxicities included testicular seminiferous tubule degeneration with consequent abnormal lumen contents in the epididymis. Microscopic findings in many tissues were consistent with the known effects of MMAE on inducing mitotic arrest (due to inhibition of tubulin formation), particularly in cells/tissues with a higher background mitotic rate.

In the repeat-dose monkey toxicology study, polatuzumab vedotin or surrogate ADC were administered once every 3 weeks (Days 1, 22, 43, 64) by IV injection resulting in doses of 1, 3, and 5 mg/kg or 3 and 5 mg/kg, respectively. Toxicities related to polatuzumab vedotin and surrogate ADC treatment included, reversible dose-dependent bone marrow hypocellularity with corresponding myelosuppression at 3 and 5 mg/kg. The surrogate ADC induced decreases in circulating B-lymphocytes (CD20+) and absence of lymphoid follicular germinal centers in the spleen at 3 and 5 mg/kg,

consistent with expected pharmacologic effects. Anti-drug-antibodies to polatuzumab vedotin or the surrogate ADC did not appear to impact exposure at any dose level and the toxicokinetic (TK) profiles were similar between ADA-positive and ADA-negative animals.

Acute and longer-term effects of MMAE administration evaluated in rats and cynomolgus monkeys included bone marrow toxicity (characterized by decreased peripheral platelets, red blood cell [RBC] and white blood cell [WBC] parameters, and decreased bone marrow cellularity), liver toxicity (characterized by elevated peripheral liver indices and hepatocellular apoptosis, necrosis, and increased mitosis), and lymphoid organ toxicity (characterized by decreased lymphoid cellularity in the thymus and spleen).

Taken together, the primary polatuzumab vedotin target organs identified by the repeat-dose toxicity studies were the bone marrow, hematolymphopoietic tissues, liver and the male reproductive organs consistent with the expected activity of MMAE.

Carcinogenicity studies in animals have not been performed with polatuzumab vedotin or MMAE and are not warranted for the proposed indication. A designated fertility study was not conducted with polatuzumab vedotin or MMAE and is not needed for the proposed indication. However, results of repeat-dose toxicity studies in rats indicate the potential for polatuzumab vedotin to impair fertility in males.

MMAE was genotoxic in the rat bone marrow micronucleus study through an aneugenic mechanism. Based on positive genotoxicity and results of general toxicology studies showing adverse effects on rapidly dividing cells, a dedicated embryofetal developmental (EFD) study with the ADC or the MMAE is not necessary, per recommendations in ICH S9. Despite this, results of EFD studies were submitted. In an embryo-fetal developmental study, pregnant rats were given 2 intravenous doses of 0.2 mg/kg MMAE during the period of organogenesis on gestation Days 6 and 13. MMAE-related toxicities included pre-/post-implantation loss and embryo-fetal lethality (early resorptions, pre-implantation and post-implantation loss, decreased numbers of live fetuses, and malformations). The fetal malformations included protruding tongue, malformed mandible corresponding to agnathia, malrotated limbs, and gastroschisis. These effects were observed at doses below the therapeutic AUC in patients who received the recommended dose of 1.8 mg/kg POLIVY every 21 days.

Based on the mechanism of action and findings from animal studies, the Warning and Precaution section of the product label will have a statement for embryo-fetal toxicity. Females of reproductive potential, and males with female partners of reproductive potential, will be advised to use effective contraception during treatment and for at least 3 and 5 months after the last dose, respectively. The recommendations for the duration for contraception are based on the FDA guidance, Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations[1], for drugs that are

[1] https://www.fda.gov/media/124829/download

aneugenic. Based on the toxicity profile of the ADC, the label will also advise women not to breastfeed during treatment and for at least 2 months (b) (4) after the last dose.

1.3 Recommendations

1.3.1 Approvability

From a Pharmacology/Toxicology perspective, approval of POLIVY is recommended for the proposed indication.

1.3.2 Additional Non Clinical Recommendations

None

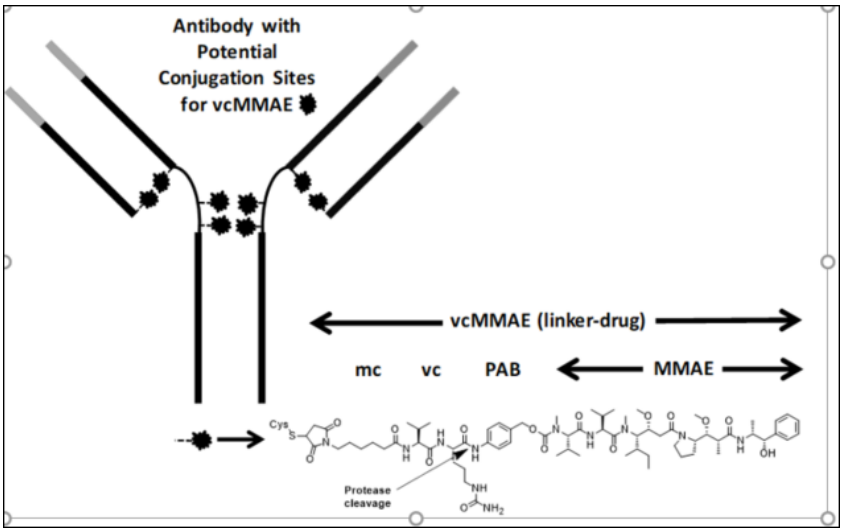
1.3.3 Labeling

The recommendations to the Applicant's proposed labeling were discussed internally and communicated to the Applicant. Information in the nonclinical sections of the label reflect findings from studies reviewed within this document and applicable guidance documents.

2 Drug Information

2.1 Drug

CAS Registry Number	1313206-42-6
Unique Ingredient Identifier	KG6VO684Z6
Generic Name	Polatuzumab vedotin
Code Name	ADC: DCDS4501A, DCDS4501S, RO5541077, pola Polatuzumab antibody intermediate: MCDS4409A SGD-1010 for the small molecule, monomethyl auristatin E (MMAE)
Other names	FCU2711, GNT-038, aCD79b-vcMMAE, MCDS4409A-VC-MMAE
Chemical Name	Immunoglobulin G1, anti-(human antigen CD79b) (human-Mus musculus monoclonal MCDS4409A heavy chain), disulfide with human-Mus musculus monoclonal MCDS4409A k-chain, dimer, thioether with maleimidocaproyl-valinecitrulline-*p*-aminobenzyloxycarbonyl monomethylauristatin E
Molecular Formula/ Molecular Weight	150 kDa
Structure or Biochemical Description	Polatuzumab vedotin is a CD79b-directed antibody-drug conjugate (ADC) consisting of three components: 1) the humanized immunoglobulin G1 (IgG1) monoclonal antibody specific for human CD79b

	2) the small molecule anti-mitotic agent MMAE 3) a protease-cleavable linker maleimidocaproyl-valine-citrulline-p-aminobenzyloxycarbonyl (mc-vc-PAB) that covalently attaches MMAE to the polatuzumab antibody. 
Pharmacologic class	CD79b-directed antibody-drug conjugate (ADC)

Polatuzumab vedotin, the surrogate ADC, and the corresponding antibodies prior to conjugation to MMAE may also be referred to the following equivalent names in the review.

Preferred Name	Description	Equivalent Names
Polatuzumab vedotin	ADC that recognizes human CD79b (used in clinical and nonclinical studies)	DCDS4501A, DCDS4501S, RO5541077, pola
Polatuzumab antibody	The antibody component of polatuzumab vedotin prior to conjugation to MMAE	MCDS4409A, polatuzumab antibody intermediate (for Module 3 documents)
Surrogate ADC	ADC that recognizes cynomolgus monkey CD79b (used in nonclinical studies only)	DCDS5017A
Surrogate antibody	The antibody component of the surrogate ADC prior to conjugation to MMAE	MCDS1358A

ADC = antibody–drug conjugate; MMAE = monomethyl auristatin E.

(Applicant table reproduced from the Pharmacology written Summary)

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 109409

2.3 Drug Formulation

POLIVY (polatuzumab vedotin) will be supplied as a sterile, white to grayish-white, preservative-free, lyophilized (b) (4) for intravenous administration after reconstitution and dilution. Each mL of reconstituted solution contains 20 mg polatuzumab vedotin.

Table 1: Composition of Polatuzumab Vedotin Drug Product

Ingredient	Target Amount per Vial[a]	Nominal Amount per Vial	Concentration[b]	Function	Specification
Polatuzumab Vedotin	(b) (4)	140 mg	(b) (4)	Active ingredient	Section S.4.1 *Specification*
Succinic Acid		8.27 mg	(b) (4)		USP-NF/JPE
Sodium Hydroxide		3.80 mg			USP-NF/Ph. Eur./JP
Sucrose		288 mg			USP-NF/Ph. Eur./JP
Polysorbate 20		8.4 mg			USP-NF/Ph. Eur./JPE

Abbreviations: JPE = Japanese Pharmaceutical Excipients; SWFI = sterile water for injection.

[a] Based on a target fill volume (b) (4)

[b] Target concentration after reconstitution with 7.2 mL of SWFI (b) (4) (b) (4)

[c] Amount to obtain a pH of 5.3.

2.4 Comments on Novel Excipients

None

2.5 Comments on Impurities/Degradants of Concern

None

2.6 Proposed Clinical Population and Dosing Regimen

POLIVY is indicated in combination with bendamustine and rituximab for the treatment of adult patients with relapsed or refractory DLBCL (see the product labeling for additional information). The proposed clinical dose of 1.8 mg/kg is to be administered to adult patients with DLBCL as an intravenous infusion over 90 minutes every 21 days for 6 cycles.

2.7 Regulatory Background

Polatuzumab vedotin has orphan drug and breakthrough therapy designations; see the clinical review.

3.3 Previous Reviews Referenced

None

4 Pharmacology

4.1 Primary Pharmacology

A. In Vitro Studies

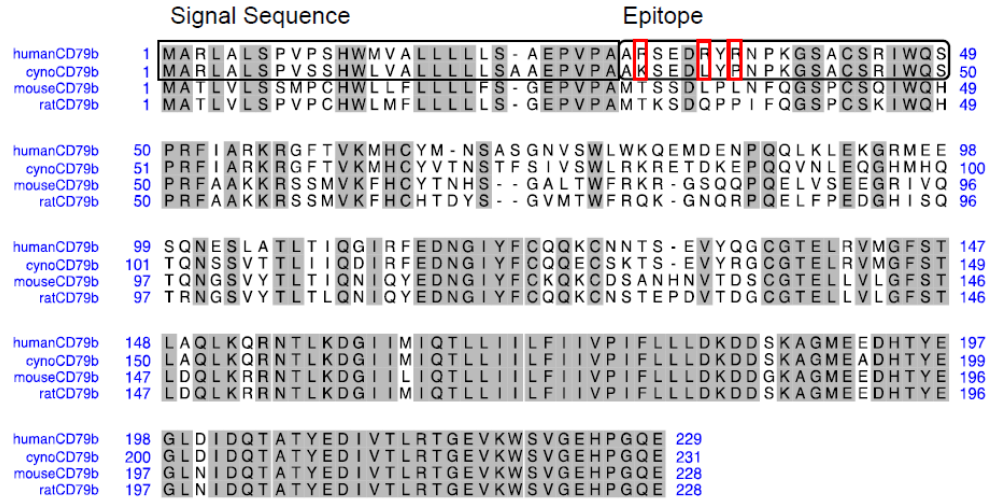
Mechanism of Action

Polatuzumab vedotin is an ADC that binds to human CD79b and delivers the anti-mitotic agent (monomethyl auristatin E [MMAE]) to B-cells. Upon binding CD79b, polatuzumab vedotin (also referred to as DCDS4501A or the "clinical ADC" in this review) is internalized within one hour.[2] It is known that ADC linkers are cleaved by lysosomal proteases, leading to intracellular release of conjugated small molecule toxicant (i.e., MMAE). The released MMAE binds to microtubules and kills dividing cells by inhibiting cell division and inducing apoptosis.

Species Relevance

Peptide sequence alignment of CD79b between humans and cynomolgus monkeys showed a variation in three amino acids in the N-terminal epitope region. Therefore, a surrogate ADC (DCDS5017A) that binds specifically to cynomolgus monkey CD79b was generated for testing target-mediated effects. The surrogate ADC consists of a chimeric mouse-human IgG1 monoclonal antibody that binds to cynomolgus monkey CD79b with the same linker and drug as polatuzumab vedotin and has a similar targeted average DAR of 3.5.

Figure 1: CD79b Protein Sequence Alignment Across Species



cyno = cynomolgus monkey.

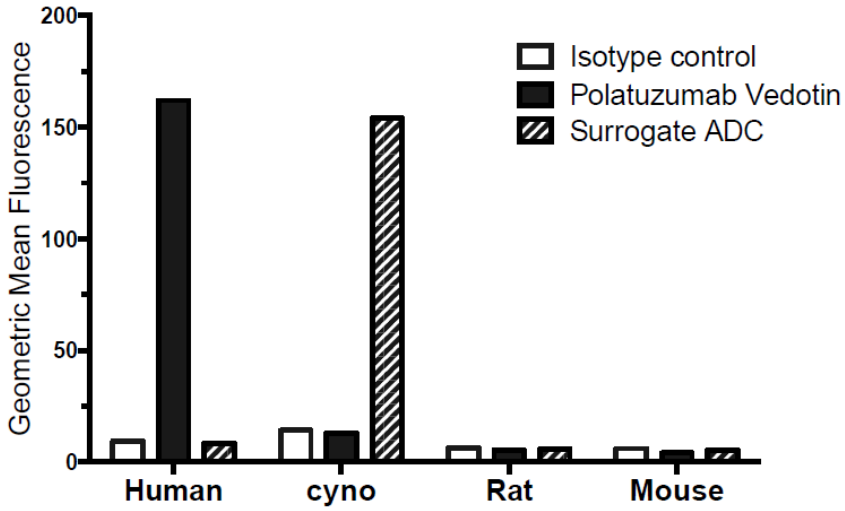
(Applicant Figure reproduced from the Pharmacology Tabulated Summary)

Binding of polatuzumab vedotin to human CD79b was demonstrated using flow cytometry of PBMC B-cell subpopulations (Study No. 10-2535). For 30 minutes, cells were incubated at room temperature (RT) with polatuzumab vedotin, surrogate ADC, or

[2] Pfeifer M, Zheng B, Erdmann T, et al. Anti-CD22 and anti-CD79B antibody drug conjugates are active in different molecular diffuse large B-cell lymphoma subtypes. Leukemia 2015;29(7):1578-86.

human anti-HER2 4D5 MC-vc-PAB MMAE (negative control) in fluorescence-activated cell sorting (FACS) buffer. Polatuzumab vedotin did not bind to CD79b on non-human primate or rodent PBMC B-cell subpopulations.

Figure 2: Binding Specificity Across Species



ADC = antibody–drug conjugate; cyno = cynomolgus monkey; PBMC = peripheral blood mononuclear cell.

(Applicant Figure reproduced from the Pharmacology Tabulated Summary)

The Applicant demonstrated comparable binding for polatuzumab vedotin, surrogate ADC, and unconjugated clinical and surrogate antibodies (MCDS4409A and MCDS1358A, respectively) in a competitive radioligand cell binding assay (Study No. 10-2298) using a human B-lymphoma BJAB stable transfected cell line co-expressing similar amounts of wild-type human CD79b and cynomolgus monkey CD79b. In this assay the CD79b antibodies in the test articles were iodinated/radiolabeled using the lactoperoxidase method, purified by gel filtration using a NAP-5 column and had comparable specific activities, ranging from 15.72 to 17.52 µCi/µg. Competition reaction mixtures of 50 µL containing a fixed concentration of iodinated antibody (60 pM) and decreasing concentrations of unlabeled antibody (1:2-fold dilution for ten concentrations, with a buffer-only sample) were placed into 96-well plates. Competition reactions were assayed in triplicate, and approximately 240,000 cells/well were added to competition reaction mixtures. Competition reactions with cells were incubated for 2 hours at RT, prior to being transferred to a Millipore Multiscreen filter plate, washed and radioactivity was measured using a gamma counter. The binding data were evaluated using New Ligand software (Genentech), which uses the fitting algorithm of Munson and Rodbard (1980) to determine the binding affinity of the antibody and the concentration of binding sites.

Table 2: Target Binding Using a Competitive Radioligand Cell Binding Assay

Species	Test Article	Dissociation Constant (Kd)
Human	DCDS4501A (polatuzumab vedotin, clinical ADC)	1.83 ± 0.26 nM
	MCDS4409A (polatuzumab "clinical" antibody)	1.33 ± 0.14 nM
Cynomolgus monkey	DCDS5017A (Surrogate ADC)	1.51 ± 0.25 nM
	MCDS1358A (Surrogate Antibody)	1.21 ± 0.10 nM

Specificity and Fc receptor binding

CD79b Expression

CD79 is the signaling component of the B-cell receptor (BCR). CD79 is a heterodimer consisting of CD79a and CD79b. It is general knowledge that CD79b-cell surface expression is restricted to normal cells within the B-cell lineage (except plasma cells) and malignant B-cells. CD79b was found to be expressed in > 95% of DLBCL samples tested (22 out of 24 samples, Dornan et al. 2009; 28 out of 28 samples in Pfeifer et al. 2015; the Applicant has the right to cross-reference both publications).

Fcγ Receptor Binding

- Polatuzumab vedotin and surrogate ADC had comparable binding affinity for FcγIA receptor. This binding affinity was also comparable to the positive control rituximab.

The polatuzumab vedotin, surrogate ADC and unconjugated clinical and surrogate antibodies bound the FcγIA receptor comparably to the rituximab positive control (average differences less than 2-fold) in an ELISA-based ligand binding assay (Study No. 10-2764). Binding to other Fcγ receptors (IIA allotypes R131 and H131, IIB, or IIIA allotypes F158 and V158) was 2- to 3-fold lower for polatuzumab vedotin (and its related antibody) compared to the surrogate ADC (and its related antibody) or rituximab. The ELISA assay utilized a panel of human Fcγ receptors, each receptor expressed as a fusion protein containing the extracellular domain of the IgG Fc binding γ chain and a Gly-6xHis-glutathione S-transferase (GST) polypeptide tag. In the assay, blocked anti-GST antibody-coated plates were incubated with Fcγ receptors at RT for 1 to 2 hours. Serial dilutions of test antibodies were added and incubated at RT for 2 hours either as monomers (for high affinity binder FcγRIA) or multimeric crosslinked antibody-$F(ab')_2$ complexes (for low affinity binders FcγRIIA, IIB, and IIIA). Plates were washed after each incubation step. Antibodies bound to the Fcγ receptors were detected with horseradish peroxidase (HRP)−conjugated anti−human F(ab′)2 antibodies, followed by the addition of substrate tetramethylbenzidine. The reaction was terminated after 5 to 30 minutes with 1 M H_3PO_4, and absorbance at 450 nm (with background at 650 nm subtracted) was measured with a microplate reader.

Table 3: EC_{50} Data of Antibodies from Individual Binding Experiments with FcγRs

Test Article	EC_{50}					
	FcγRIA (ng/mL)	FcγRIIA-H131 (μg/mL)	FcγRIIA-R131 (μg/mL)	FcγRIIB (μg/mL)	FcγRIIIA-F158 (μg/mL)	FcγRIIIA-V158 (μg/mL)
Rituximab	6.89±2.01	0.457±0.0739	1.42±0.448	2.03±0.144	2.72±0.0404	0.618±0.168
Polatuzumab Vedotin	9.46±2.37	3.15±0.204	5.13±0.543	7.81±0.728	7.39±1.56	1.82±0.272
Polatuzumab Antibody	12.4±3.18	2.76±0.466	8.11±1.08	9.53±0.110	6.52±1.38	1.23±0.247
Surrogate ADC	8.53±2.17	1.49±0.121	1.96±0.276	2.98±0.137	2.34±0.289	0.714±0.147
Surrogate Antibody	10.7±3.02	1.24±0.119	2.98±0.690	3.77±0.319	2.02±0.244	0.547±0.102

ADC = antibody–drug conjugate; EC_{50} = half-maximal effective concentration (the effective concentration of the antibody at which 50% of the maximum response from binding to the FcγR was detected); FcγR = Fc gamma receptor.

Notes: Each value represents the average of three independent experiments ± the standard deviation of those experiments.

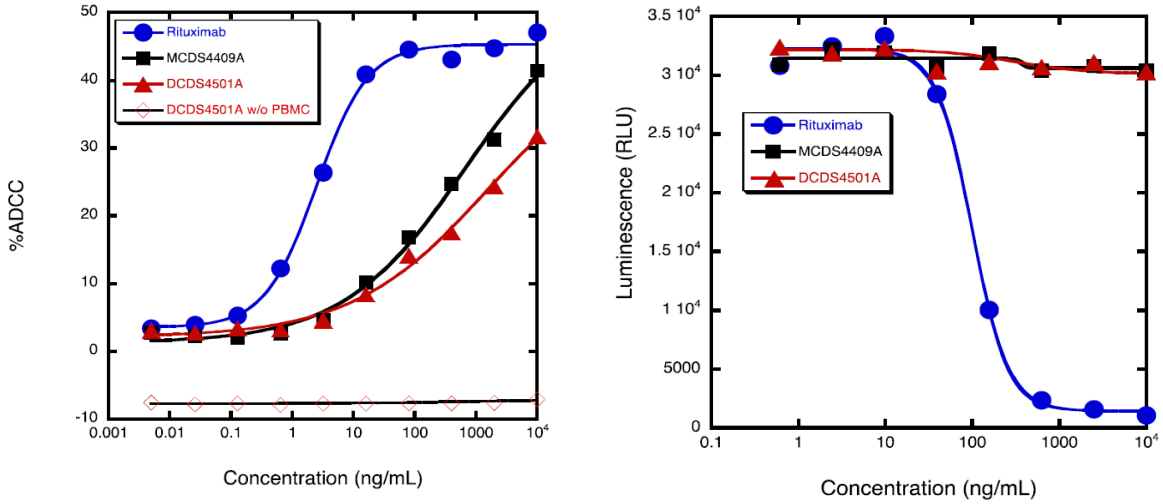
(Applicant Figure reproduced from the Pharmacology Tabulated Summary)

ADCC and CDC Activity

- Polatuzumab vedotin had no CDC activity. It had ADCC activity that was substantially lower than that of the positive control, rituximab.
- The surrogate ADC was not tested for ADCC or CDC activity.

The ADCC activity of polatuzumab vedotin (and its antibody) was assessed using target cells and purified effector PBMCs from healthy human donors. The ADCC activity was one order of magnitude (1000-fold) lower for polatuzumab vedotin and its antibody compared with rituximab. The half minimal effective concentration (EC_{50}) for rituximab was approximately 5 ng/mL (Study No. 10-2764). In the ADCC assay, PBMCs were verified as viable and blood donors were limited to those carrying the heterozygous FcγRIIIA genotype (F/V158). In this assay, polatuzumab vedotin or unconjugated clinical antibody were added at concentrations ranging from 10,000 to 0.0051 ng/mL in 50 µL to pre-seeded wells (4×10^4 target BJAB cells) and incubated at 37° C for 30 minutes. After the incubation, 1.0×10^6 PBMC effector cells (isolated by density gradient centrifugation) in 100 µL of assay medium were added to each well to give a ratio of 25:1 effector-to-target cells, and the plates were incubated for an additional 4 hours. The plates were centrifuged at the end of incubation and the readout for cytotoxicity in the ADCC assay was lactate dehydrogenase activity in the supernatants. The reaction was terminated after 15 minutes. In addition, no CDC was observed in BJAB cells (10^5 cells/well), incubated for 2 hours at 37° C with polatuzumab vedotin or unconjugated clinical antibody (1 to 10,000 ng/mL) with complement derived from rabbit serum (diluted 1:3 in assay medium). The readout for cytotoxicity was the same as in the cell proliferation assay with Cell Titer Glo II™ (see below). CDC was observed with the positive control, rituximab. The surrogate molecules (MCDS1358A and DCDS5017A) were not tested for ADCC or CDC activity due to unavailability of cynomolgus monkey cell lines.

Figure 3: ADCC and CDC Activity for Polatuzumab Vedotin and Antibody



ADCC = antibody-dependent cell-mediated cytotoxicity; DCDS4501A = polatuzumab vedotin; MCDS4409A = polatuzumab antibody; PBMC = peripheral blood mononuclear cells; w/o = without. CDC = complement-dependent cytotoxicity; RLU = relative luminescence unit.

(Applicant Figures reproduced from the Pharmacology Tabulated Summary)

Cytokine Release Assay

Cytokine release induced by the polatuzumab (clinical) antibody when incubated with human PBMCs was minimal, with only 2 (IP-10 and IL-1α) of the 30 cytokines showing an increase, but the increase was less than the level observed following exposure to the CD3 (OKT3) positive control (Study No. 10-2299). No other cytokines evaluated in human PBMC experiments (eotaxin, G-CSF, GM-CSF, IFN-α2, IFN-γ, IL-1β, IL-1ra, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12 p40, IL-12 p70, IL-13, IL-15, IL-17, MCP-1, MIP-1α, MIP-1β, soluble CD40 ligand, TGF-α, TNF-α, TNF-β, and VEGF) were elevated above the levels observed following exposure to the negative control antibody (trastuzumab).

In Vitro Anti-Tumor Activity

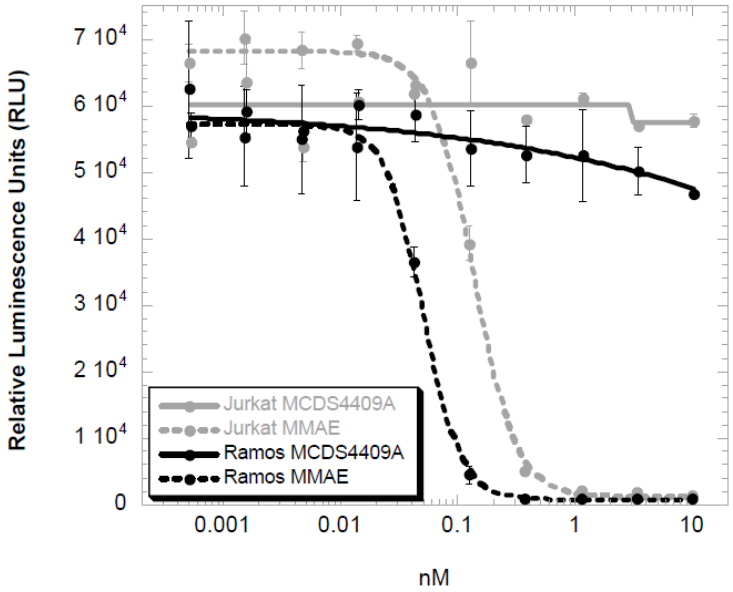
In a cell-based anti-proliferation assay (Study No. 10-2308), polatuzumab vedotin reduced cell viability of CD79b-positive human Burkitt lymphoma cell line (Ramos) after 3 days incubation at 37ºC with a half-maximal inhibitory concentration [IC_{50}] equal to 0.071 ± 0.014 nM. Only the highest concentration tested (10 nM) reduced cell viability in a CD79b-negative human T-cell leukemia cell line (Jurkat). In the assay, 50 µL of the polatuzumab vedotin and antibody or MMAE dilutions were assayed in duplicate to cell-seeded wells (2000 cells/well) with final concentrations ranging from ~ 0.5 pM to 10 nM. One set of duplicate wells received culture medium without test article. Cell viability was assessed by measuring levels of adenosine 5′-triphosphate (ATP) released from lysed/killed cells with Cell Titer Glo II™. The extent of cell lysis was quantified by measuring intensity of luminescence with a plate reader. Target expression of CD79b on Ramos, but not Jurkat cells, was confirmed with flow cytometry. A negative conjugate control, trastuzumab MC-VC-PAB MMAE did not show anti-proliferative activity (data not shown).

Table 4: IC_{50} for Polatuzumab Vedotin in Ramos and Jurkat Cells

Test Article	Ramos	Jurkat
DCDS4501A (polatuzumab vedotin, clinical ADC)	0.071 ± 0.014 nM	NA
MCDS4409A (polatuzumab "clinical" Antibody)	NA	NA
MMAE	0.075 ± 0.024 nM	0.13 ± 0.089 nM

NA = not applicable (IC_{50} values were not calculated since there was no cell killing up to the highest concentration tested);

Figure 4: Anti-Proliferative Activities of the Polatuzumab Antibody and MMAE



MMAE = monomethyl auristatin E.
Note: Serial dilutions of MCDS4409A and MMAE were applied to Ramos and Jurkat cells to the final concentrations as shown on the graph (on a log 10 scale). The graph shows one representative experiment in which each point is an average of duplicate values.

(Applicant Figure reproduced from Study 10-2308)

Polatuzumab vedotin was also shown to be active in human DLBCL cell lines with a wide range of surface CD79b expression, including both activated B-cell and germinal center B-cell subtypes.[3]

B. In Vivo Studies

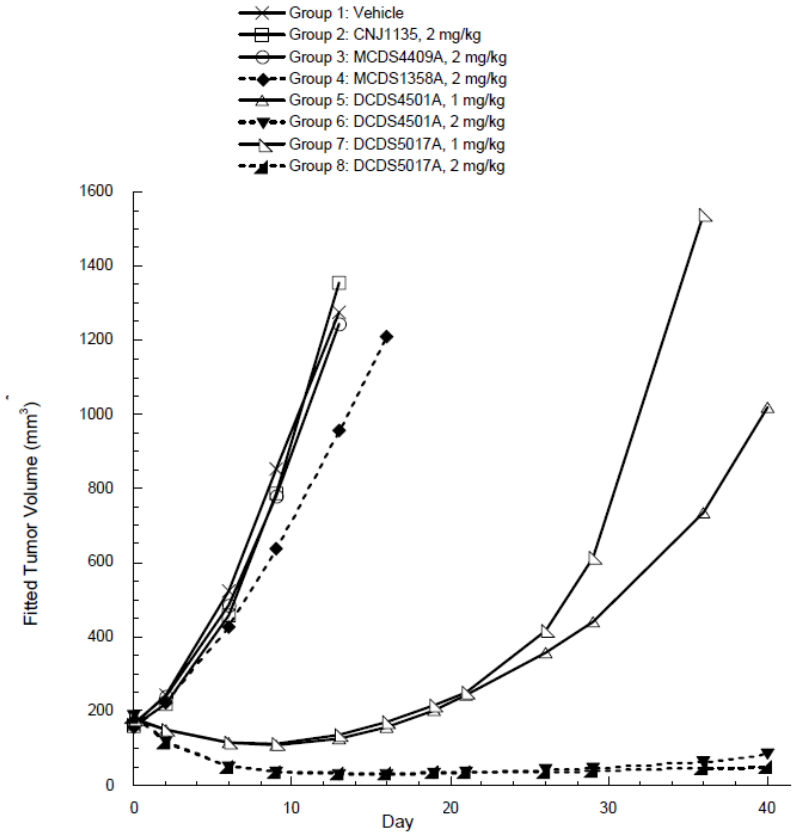
For all xenograft studies described below, tumor cells were injected subcutaneously (2 x 10^7 cells in 0.2 mL) into the right flank area. Partial responses (PR) are defined as a tumor regression of > 50% but < 100% of the starting tumor volume, and complete responses (CR) are defined as 100% tumor regression (i.e., no measurable tumor) on any day during the study.

To assess the in vivo anti-tumor activity of polatuzumab vedotin, the Applicant conducted mouse xenograft studies. In one study (Study No. 09-0406B), female C.B-17 Fox Chase severe combined immunodeficiency (SCID) mice were injected subcutaneously with BJAB-PD.cyCD79b.E3 tumor cells (BJAB cells stably expressing

[3] See footnote 1.

similar amounts of surface cynomolgus monkey and human CD79b). When tumors reached a volume in the range of 117−214 mm^3, animals were randomized into eight groups of 10 mice each and given a single intravenous injection (5 mL/kg) of vehicle control (histidine buffer), 1 to 2 mg/kg of polatuzumab vedotin or surrogate ADC, or 2 mg/kg of the clinical or surrogate antibodies, or conjugate control (Anti-Her2-MC-VC-PAB-MMAE) (Day 0 of the study). A single 2 mg/kg dose of the polatuzumab vedotin or surrogate ADC resulted in tumor growth inhibition (TGI) of ~125% (TGI is defined as $\%TGI = 100x\left[1-\left(\frac{AUC_{treatment}/day}{AUC_{vehicle}/day}\right)\right]$). Five of the 10 mice given 2 mg/kg polatuzumab vedotin and 7 of the 10 mice given 2 mg/kg of the surrogate ADC maintained CRs until the end of study.

Figure 5: Growth Inhibition of BJAB-PD.cyCD79b.E3 Xenograft Tumors in Response to a Single Dose of Polatuzumab Vedotin and other Test Articles



ADC = ant body drug conjugate; CNJ1135 = anti-Her2-mc-vc-PAB-MMAE (control ADC); DCDS4501A = polatuzumab vedotin; DCDS5017A = surrogate ADC; MCDS1358A = surrogate antibody; MCDS4409A = polatuzumab antibody. Note: All test materials were administered by intravenous injection through the tail vein once on Day 0.

(Applicant Figure reproduced from Study 09-0406B)

In a different SCID xenograft model (Study No. 09-0406D), the anti-tumor activity of polatuzumab vedotin and antibody against human DLBCL WSU-DLCL2 cells was measured in mice. When tumors reached a volume of 101-197 mm^3, animals were randomized into eight groups of 8 mice each and given a single intravenous injection of

test materials (Day 0 of the study). Group 1 received histidine buffer as a vehicle control, Group 2 received 12 mg/kg anti-Her2-mc-vc-PAB-MMAE (non-binding control ADC), and Group 3 received 12 mg/kg polatuzumab antibody (adminstration was IV with a dose volume of 5 mL/kg in all groups). Groups 4-8 received 0.3, 1, 3, 6, or 12 mg/kg polatuzumab vedotin, respectively. At doses of 6 and 12 mg/kg polatuzumab vedotin, respectively, CRs were observed for 3/8 (~38%) and 7/8 (~88%) of mice. Six out of 8 of the 12 mg/kg polatuzumab vedotin mice maintained CRs through the end of the study (Day 49). The mean maximum plasma concentration at 12 mg/kg polatuzumab vedotin, was 100 µg/mL.

Table 5: Response of WSU-DLCL2 Xenograft Tumors to a Single Dose of Polatuzumab Antibody (MCDS4409A), Non-binding control ADC (CNJ1135), or Polatuzumab Vedotin (DCDS4501A)

Group	Test Material	Dose (mg/kg)	PR [a]	CR [b]	Fitted Tumor Volume (mm^3) Day 18	AUC/day %TGI [c] Day 18	TTD [d] (Day)
1	Vehicle	NA	0	0	1489	0	3.5
2	CNJ1135	12	0	0	957	41	5.5
3	MCDS4409A	12	0	0	1180	34	5.5
4	DCDS4501A	0.3	0	0	1123	30	5.0
5	DCDS4501A	1	0	0	786	62	8.5
6	DCDS4501A	3	2	0	173	101	21.5
7	DCDS4501A	6	1	3	38	115	38.0
8	DCDS4501A	12	1	7	10	120	> 49

AUC = area under the fitted curve; CR = complete response; NA = not applicable; PR = partial response; TGI = tumor growth inhibition; TTD = time to tumor doubling.

[a] Tumor volume regressed 50%–99% from its initial (Day 0) volume.

[b] 100% tumor regression.

[c] The difference between the AUC/day of the treatment and vehicle groups, divided by the AUC/day in the vehicle group, expressed as a percentage.

[d] Time (in days) required for tumors to double in size, compared with the initial (Day 0) fitted volume of the vehicle group.

(Applicant Table reproduced from Study 09-0406D)

In a xenograft study (Study No. 14-3262B), SCID mice were injected with human DLBCL WSU-DLCL2 cells using similar methods as the other studies. When tumors reached an average size of 117 mm^3 in volume, animals were randomized into six groups of 7 mice each and given polatuzumab vedotin, obinutuzumab, cyclophosphamide (C), doxorubicin (H), prednisone (P), and bendamustine according to the table below. While all test articles resulted in TGI nearing 100%, combining polatuzumab vedotin with obinutuzumab plus chemotherapy produced more durable activity than either alone with a time to tumor doubling of 24.5 days plus CHP and >27 days plus bendamustine compared to 3.5 days for vehicle controls (see Table below).

Two PRs were observed for polatuzumab vedotin with obinutuzumab plus bendamustine, but no CRs were observed in this study.

Table 6: Anti-DLBCL Tumor Activity of Polatuzumab Vedotin

Group	Test Material[a]	Dose (mg/kg)	Route	Dose Frequency	Days of Dosing	PR[b]	TTD[c]	Day 14 %TGI[d] (Lower, Upper)[e]
1	PBS	NA	IP	Once	Day 0	0	3.5	0 (0, 0)
	Histidine buffer		IV	Once	Day 0			
	Saline		PO	Daily x 5	Days 0-4			
2	Polatuzumab vedotin	2	IV	Once	Day 0	0	18.5	96 (86, 104)
3	Obinutuzumab	30	IP	Once	Day 0	0	11	81 (62, 93)
	Cyclophosphamide	30	IV	Once	Day 0			
	Doxorubicin	2.475	IV	Once	Day 0			
	Prednisone	0.15	PO	Daily x 5	Days 0-4			
4	Obinutuzumab	30	IP	Once	Day 0	1	16	102 (93, 110)
	Bendamustine	30	IV	Once	Day 0			
5	Obinutuzumab	30	IP	Once	Day 0	1	24.5	104 (96, 112)
	Cyclophosphamide	30	IV	Once	Day 0			
	Doxorubicin	2.475	IV	Once	Day 0			
	Prednisone	0.15	PO	Daily x 5	Days 0-4			
	Polatuzumab vedotin	2	IV	Once	Day 0			
6	Obinutuzumab	30	IP	Once	Day 0	2	> 27	110 (104, 119)
	Bendamustine	30	IV	Once	Day 0			
	Polatuzumab vedotin	2	IV	Once	Day 0			

IP = intraperitoneal; IV = intravenous; PO = oral; AUC = area under the fitted curve; NA = not applicable; PR = partial response; TGI = tumor growth inhibition; TTD = time to tumor doubling; UI = uncertainty interval;
a Cyclophosphamide and doxorubicin were combined and given as a single IV injection. For combination groups, test materials were administered in the order listed, immediately after each other.
b Tumor volume regressed 50%-99% from its initial (Day 0) volume.
c Time (in days) for a tumor to double in volume from Day 0.
d % TGI = 100 x [1 - ($AUC_{treatment}$ per day / $AUC_{vehicle}$ per day)], calculated at the last day the vehicle control group was present.
e Lower and upper limits of the 95% UI for % TGI.

The anti-tumor activity of polatuzumab vedotin in combination with rituximab plus chemotherapy was evaluated in a tumor xenograft model of human DLBCL WSU-DLCL2 in SCID mice (Study No. 13-0599). Animals were distributed into seven groups of 9 mice each so that the tumor volume distribution was similar across groups. Combining polatuzumab vedotin with rituximab plus chemotherapy (CHP or bendamustine) produced more durable activity (with a TTD of 35 and 32.5 days, respectively) than either polatuzumab vedotin alone or the combination of rituximab plus chemotherapy.

Table 7: Anti-Tumor Activity of Polatuzumab in Vedotin in WSU-DLCL2 DLBCL

Group	Test Material[a]	Dose (mg/kg)	Route	Dose Frequency	PR/CR[b]	TTD[c]	Day 17 %TGI[d] (Lower, Upper)[e]
1	PBS	NA	IP	Once	0/0	5.0	0 (0, 0)
	Histidine buffer		IV	Once			
	Saline		PO	Daily x 5			
2	Polatuzumab vedotin	2	IV	Once	0/1	21.0	107 (99, 121)
3	Rituximab	30	IP	Once	0/0	13.5	80 (54, 94)
	Cyclophosphamide	30	IV	Once			
	Doxorubicin	2.475	IV	Once			
	Vincrisitine	0.375	IV	Once			
	Prednisone	0.15	PO	Daily x 5			
4	Rituximab	30	IP	Once	0/0	9.5	66 (25, 85)
	Cyclophosphamide	30	IV	Once			
	Doxorubicin	2.475	IV	Once			
	Prednisone	0.15	PO	Daily x 5			
5	Rituximab	30	IP	Once	3/0	18.0	102 (91, 114)
	Bendamustine	30	IV	Once			
6	Rituximab	30	IP	Once	1/1	35.0	108 (100, 120)
	Cyclophosphamide	30	IV	Once			
	Doxorubicin	2.475	IV	Once			
	Prednisone	0.15	PO	Daily x 5			
	Polatuzumab vedotin	2	IV	Once			
7	Rituximab	30	IP	Once	1/1	32.5	107 (98, 119)
	Bendamustine	30	IV	Once			
	Polatuzumab vedotin	2	IV	Once			

IP = intraperitoneal; IV = intravenous; PO = oral; AUC = area under the fitted curve; NA = not applicable; PR = partial response; CR = complete response; TGI = tumor growth inhibition; TTD = time to tumor doubling; UI = uncertainty interval;
a Cyclophosphamide, doxorubicin, and vincristine were combined and given as a single IV injection. For combination groups, test materials were administered in the order listed, immediately after each other.
b Tumor volume regressed 50%-99% from its initial (Day 0) volume for PR and 100% tumor regression (i.e., no measurable tumor) for CR.
c Time (in days) for a tumor to double in volume from Day 0.
d % TGI = 100 x [1 - ($AUC_{treatment}$ per day / $AUC_{vehicle}$ per day)], calculated at the last day the vehicle control group was present.
e Lower and upper limits of the 95% UI for % TGI.

4.2 Secondary Pharmacology

No studies were submitted under secondary pharmacology.

4.3 Safety Pharmacology

MMAE alone did not appreciably inhibit the human ether-à-go-go-related gene (hERG) channel (IC_{50} > 100 µM) in voltage-clamped human embryonic kidney cells (Study No. 07-0611; GLP-compliant). The positive control (60 nM terfenadine) inhibited hERG potassium current by 84.0 ± 0.4% (Mean ± SD; n = 2).

Neurobehavioral, motor activity, and ophthalmic assessments were included in the 4-week repeat-dose toxicology study in rats, using polatuzumab vedotin (Study 10-0898). Cardiovascular, respiratory, and neurologic assessments were included in the 10-week repeat-dose toxicology study in cynomolgus monkeys, using polatuzumab vedotin or the surrogate ADC (10-0044). These studies are reviewed below.

5 Pharmacokinetics/ADME/Toxicokinetics

Absorption
Characterization of the Pharmacokinetics of Naked SN8 (MCDS4409A), SN8-vc-MMAE (DCDS4501A), Naked 10D10 (MCDS1358A), and 10D10-vc-MMAE(DCDS5017A) in Female SCID Mice/ # 10-1571 Methods/Readout: 33 female mice/group. Antibody levels (conjugated and unconjugated) were measured with a semi-homogeneous assay (SHA) using a human (Groups 1 and 2) or cynomolgus monkey (Groups 3 and 4) 15-amino acid peptide for capture and a biotinylated goat anti-human Fc antibody conjugated with horseradish peroxidase (HRP) for detection. The ADCs were detected with ELISA. Antibody-Conjugated MMAE was measured using (b) (4) affinity capture from plasma and followed by enzyme-mediated release of MMAE and electrospray ionization liquid chromatography tandem mass spectrometry (LC/MS/MS) for detection. Results: The PK profiles of total antibody following single IV administration of polatuzumab vedotin or the surrogate ADC were similar between the two ADCs and were characterized by a short distribution phase and a long elimination phase, as expected for a monoclonal antibody-based therapeutic.

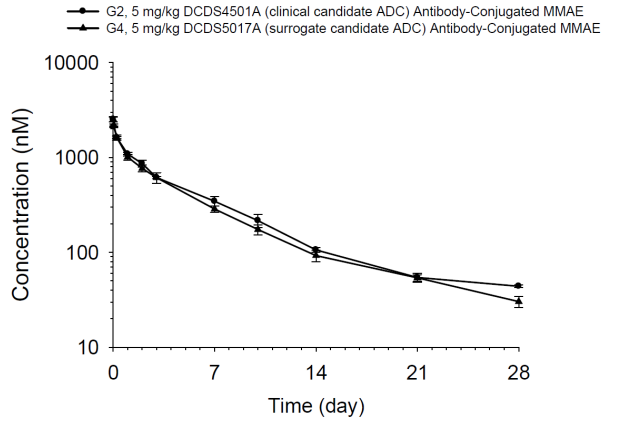
PK Parameter	Group 1 5 mg/kg MCDS4409A [a] MCDS4409A	Group 2 5 mg/kg DCDS4501A [b] Total Antibody	Group 3 5 mg/kg MCDS1358A [c] MCDS1358A	Group 4 5 mg/kg DCDS5017A [d] Total Antibody
C_{max} (µg/mL)	112±3.40	114±3.99	100±2.97	96.5±2.26
AUC (day•µg/mL)	1800±113	983±44.8	1030±53.3	715±23.3
CL (mL/day/kg)	2.78±0.175	5.09±0.232	4.84±0.250	6.99±0.228
$t_{1/2, \alpha}$ (day)	0.115±0.0205	0.131±0.0276	0.220±0.0399	0.294±0.0470
$t_{1/2, \beta}$ (day)	22.4±1.82	11.8±0.753	15.4±1.13	10.5±0.533
V_1 (mL/kg)	44.6±1.35	44.0±1.54	50.0±1.48	51.8±1.21
V_{ss} (mL/kg)	89.5±2.58	85.8±3.02	106±3.71	102±3.11
C_{max}/D (kg • µg/mL/mg)	22.4	22.7	20.0	19.3
AUC/Dose (day • kg • µg/mL/mg)	360	197	207	143

ADC=antibody–drug conjugate; AUC=area under the plasma concentration–time curve (A/α+B/β); AUC/Dose=area under the plasma concentration–time curve normalized by dose; C_{max}=maximum observed concentration; C_{max}/Dose=maximum observed concentration normalized by dose; CL=clearance (Dose/AUC_{inf}); IV=intravenous; PK=pharmacokinetic; $t_{1/2, \alpha}$=half-life of the alpha phase (ln(2)/α); $t_{1/2, \beta}$=half-life of the beta phase (ln(2)/β); V_1=volume of distribution of the central compartment (Dose/(A+B)); V_{ss}=volume of distribution at steady state (MRT_{inf} • CL).

[a] Clinical candidate antibody.
[b] Clinical candidate ADC.
[c] Surrogate antibody.
[d] Surrogate ADC.

(Applicant Table reproduced from Study 10-1571)

- Antibody conjugated concentrations of MMAE were also comparable for the two ADCs.



Lower limit of quantitation=0.195 nM.

(Applicant Figure reproduced from Study 10-1571)

Distribution

Determination of Tissue Distribution of DCD4501A (Anti-CD79b-vc-MMAE) following IV Administration of [125I]/[111In]-Anti-CD79b-vc-MMAE in Female Sprague-Dawley Rats/ # 14-0596

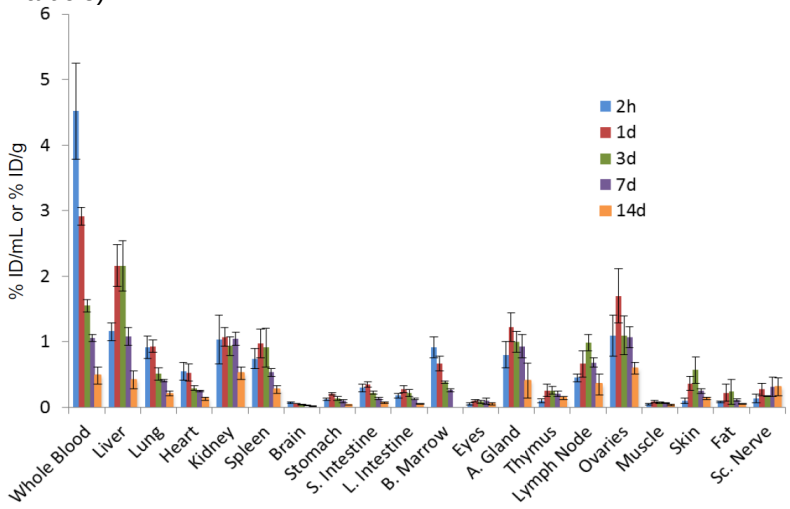
Methods/Readout: femoral vein-cannulated female Sprague-Dawley rats were divided into four groups (Groups 1-4) of 15 rats each. Tissue distribution was detected with iodine-125 ([125I])- or DOTA-indium-111 ([111In])-labeled polatuzumab vedotin and polatuzumab antibody. Following single IV bolus doses, blood and various tissues were collected at multiple intervals up to 14 days post-dose. All samples were analyzed using a gamma counter and a few plasma samples were also analyzed using an in-line SEC-HPLC radio-detector. The blood and tissue radioactivity data were calculated as percentage of injected dose (ID) normalized by blood volume (% ID/mL) or tissue weight (% ID/g).

Group	No./Sex	Route	Molecule Dosed	[^{125}I] Radioactivity Level (μCi/kg)	[^{111}In] Radioactivity Level (μCi/kg)	Unlabeled Molecule Dose Level (mg/kg)	Dose Volume (mL)
1	15/F	IV	DCDS4501A	48	48	0	0.5
2	15/F	IV	DCDS4501A	48	48	10	0.5
3	15/F	IV	MCDS4409A	48	48	0	0.5
4	15/F	IV	MCDS4409A	48	48	10	0.5

Ci = curie; [^{125}I] = iodide-125; [^{111}In] = indium-111; IV = intravenous.

Results:

- Radiolabeled DCDS4501A cleared faster than radiolabeled MCDS4409A (either as tracer alone or tracer plus unlabeled materials. Overall, the tissue distribution of DCDS4501A and MCDS4409A was non-specific (i.e., did not change dramatically when adding unlabeled test article).



[^{111}In] = indium-111; A. = adrenal; B. = bone; d = day; ID = injected dose; h = hour; IV = intravenous; L. = large; S. = small; Sc. = sciatic.

(Applicant Figure for Radioactivity Levels (% ID/g or % ID/mL) of DCDS4501A with Tracer Alone over the Course of the Study reproduced from Study 14-0596)

.

Characterization of Catabolism, Tissue Distribution, and Route of Elimination of DCDS4501S (Anti-CD79b-vc-MMAE) following IV Administration of Anti-CD79b-vc-[3H]MMAE in Normal Sprague-Dawley Rats/ # 14-2852

Methods/Readout: Fifteen female Sprague-Dawley rats weighing approximately 200 g each were given an IV bolus dose of polatuzumab vedotin-[3H]MMAE mixed with unlabeled polatuzumab vedotin at 10 mg/kg (equivalent to 150 µCi/kg radioactivity). Radioactivity was measured using liquid scintillation counting of blood or homogenized and solubilized tissue samples. Of those 15 rats, 6 rats were housed in metabolism cages for collection of urine and feces. The other 9 rats were kept in regular cages for collection of blood and tissue samples.

Results:

- Elimination was biphasic.
- Polatuzumab vedotin was identified as the major species in circulation, as opposed to low molecular weight catabolites.
- As in the previous study, polatuzumab vedotin was nonspecifically distributed to various tissues, especially to highly perfused tissues where it underwent various levels of catabolism.
- The catabolites of polatuzumab vedotin were mainly eliminated via a biliary−fecal route (103%± 11.8% injected dose), with minor elimination through renal excretion (5.21%± 1.03%

injected dose).

- Mass balance was achieved, indicating that the elimination was complete in rats over the 14-day study period.

Metabolism

In Vitro Plasma Stability Evaluation of DCDS4501A and DCDS5017A in Human and Animal Plasma/ # 10-1636

Methods/Readout: DCDS4501A , DCDS5017A, MCDS1358A , and MCDS4409A at 100 µg/mL were incubated at 37°C with vehicle, or human, cynomolgus monkey, rat, or mouse plasma for 0, 6, 24, 48, or 96 hours. Total antibody levels and free MMAE levels were measured.

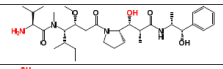
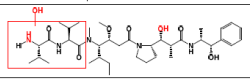
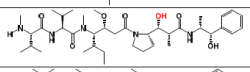
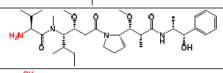
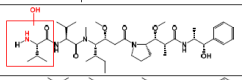
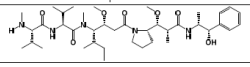
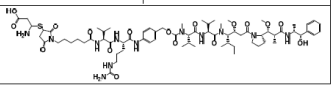
Results:
Apart from mouse samples (in which the surrogate ADC was less stable than in other species), the total antibody concentration was roughly similar for both conjugates in all samples, with all samples other than vehicle decreasing ~25% by 96 hours. Free MMAE at 96 hours was similar for both conjugates in all species with cynomolgus monkey and human samples showing no significant increase, 5x increase of MMAE in rat plasma compared to control for the clinical and nonclinical surrogate antibodies, and approximately 66x increase of MMAE in mouse plasma (~25% of theoretical MMAE present in the conjugate).

Excretion

Determination of Excretion and Catabolite Profile of DCDS4501S (Anti-CD79b-vc-MMAE) in Bile following a Single IV
Administration of Anti-CD79b-vc-[3H]MMAE in Bile Duct Cannulated Female Sprague-Dawley Rats/ # 14-2851 (amended as study 16-2563)

Methods/Readout: The catabolism of polatuzumab vedotin was characterized following a single IV bolus injection of polatuzumab vedotin at 10 mg/kg with tritium-labeled MMAE (aka polatuzumab vedotin-[3H]MMAE) in female Sprague-Dawley rats. Plasma, urine, and bile samples from Studies 14-2851 and 14-2852 were analyzed by radioprofile, LC-MS, and LC-MS/MS to characterize the catabolite profile and identify the catabolites.

Results:

Catabolite	Mass (Da)	Retention Time (min)	% Dosed (Urine)	% Dosed (Bile)	% Dosed (Urine+Bile)	Matrix	Structure
C1	NA	5.3	2.26	NA	2.26	Urine	Unknown
C2: Amide hydrolysis+ *O*-demethylation	590.40	14.9	NA	3.94	3.94	Bile	
C3: *O*-, *N*-demethylation+ OH	705.47	16.8	NA	9.32	9.32	Bile	
C4: *O*-demethylation (-CH3)	703.48	18.5	NA	13.49	13.49	Bile	
C5: Amide hydrolysis	604.42	19.5 [a]	NA	12.16 [b]	12.16 [b]	Bile	
C6: *N*-demethylation+ hydroxylation	719.48		NA			Bile	
C7: MMAE	717.50	21.6	2.56	16.48	19.04	Plasma, Urine, Bile	
C8: Cys-vc-MMAE	1436.79	34.3	NA	2.60	2.60	Bile	

(Applicant Figure for MMAE-Related Metabolites in Pooled Rat Urine and Bile following a Single Intravenous Dose of Polatuzumab Vedotin-[3H]MMAE reproduced from the Pharmacology Written Summary (Study No.16-2563))

The major catabolites of DCDS4501S identified in rats were unconjugated MMAE (in all three matrices [occurring at 2.56% and 16.5% of dose in urine and bile, respectively]), O-demethylated MMAE (in bile at 13.5% of dose), and amide hydrolysis and N-demethylation with hydroxylation (in bile at 12.2% of dose).

Other

Pharmacokinetic Comparability of Polatuzumab Vedotin (v0.1-Derived Drug Product and v1.0-Derived Drug Product) in Female Sprague Dawley Rats/ # 18-0268

Methods/Readout: Female Sprague Dawley rats (15 weeks old and weighing approximately 236-279 g each) were assigned to two groups. Rats were administered a single IV dose of polatuzumab vedotin v0.1, clear colorless liquid (lot no. 669260)- or v1.0, white to greyish white lyophilized powder (lot no. 3217347)-derived materials at a nominal dose of 6 mg/kg (concentration of 1.2 mg/mL in dose volume of 5 mL/kg) (n = 25 rats/group). Rat plasma was sampled for systemic PK up to Day 28 and concentrations of both total antibody and conjugated MMAE in rat plasma were determined using qualified immunoassay LC-MS/MS methods. Concentration-time data for each treatment group (v0.1 and v1.0) were analyzed by noncompartmental PK analysis to determine key PK parameters; bioequivalence (BE) analysis was performed using the v0.1-derived drug product as the reference material.

Results:

- The PK profiles of total antibody and MMAE were comparable between the two drug products. The two materials, v0.1 and v1.0, were bioequivalent (BE criteria of 0.8-1.25 with 90% CI) in rats with respect to the AUC_{last} and C_{max} for both total antibody and MMAE.

Polatuzumab Vedotin Analyte	PK Parameter	Group 1 (v0.1) Geometric Mean	Group 2 (v1.0) Geometric Mean	v1.0 Relative to v0.1 Material	
				Geometric Mean Ratio	90% CI
Total Antibody	C_{max} (µg/mL)	128	132	1.03	0.987-1.07
	AUC_{last} (day*µg/mL)	563	554	0.984	0.927-1.04
Antibody-conjugated MMAE	C_{max} (ng/mL)	2230	2340	1.05	1.02-1.09
	AUC_{last} (day*ng/mL)	3690	3740	1.01	0.973-1.05

(Applicant Table reproduced from Study No. 18-0268)

6 General Toxicology

6.1 Single-Dose Toxicity

The acute toxicologic effects of MMAE administered by a single intravenous bolus tail-vein injection were assessed in rats at 0.206 mg/kg (Study 03-0202) or 0.516 mg/kg (Study 03-0315) and monkeys at 0.116 mg/kg (SNBL.163.19) and at 0.03 and 0.063 mg/kg at (Study 07-0609).

Rats

- Bone marrow toxicity was associated with mortality and morbidity in males at 0.516 mg/kg.
- Dose-dependent bone marrow toxicity (decreased total WBCs and platelets, decreased bone marrow cellularity), liver toxicity (increased AST, ALT, GGT, and total bilirubin, as well as increased mitosis, apoptosis, and necrosis), and lymphoid organ toxicity (decreased lymphocyte cellularity in the thymus and spleen).

Monkeys

- Bone marrow toxicity was associated with mortality and related opportunistic infection (lung abscess) in males at 0.063 mg/kg.
- Significant reductions in WBCs, erythrocytes, hemoglobin, hematocrit, and reticulocytes, albumin and slight elevations in AST.
- Decreased bone marrow cellularity and decreased lymphocyte cellularity and necrosis in the thymus, spleen, and rectal gut-associated lymphoid tissue (GALT).

6.2 Repeat-Dose Toxicity

Study Title/number: Multiple-Dose Toxicity and Toxicokinetic Study of DCD4501A Administered Intravenously to Sprague-Dawley Rats Once Weekly for Four Doses Followed by a 6-Week Recovery Period/ 10-0898

Key findings:

- Toxicities were observed mainly in the hematopoietic/ lymphoid system, liver, skin, GI tract, and reproductive organs.

Sprague-Dawley rats (15M/15F) were given 2, 6, and 10 mg/kg polatuzumab vedotin (DCDS4501A) administered weekly for a total of 4 doses with a 6-week recovery period to assess the antigen-independent toxicity/toxicokinetics.

Results:

- One 10 mg/kg male was euthanized in moribund condition during recovery due to marked anemia with corresponding microscopic findings of decreased bone marrow cellularity associated with hematology changes; and, hepatic centrilobular degeneration associated with increases in aspartate and alanine aminotransferase.

- Increased incidence of low arena locomotor activity was noted during the dosing phase in males (4/10 versus 1/10 controls) at 10 mg/kg (measured by functional observational battery). These animals recovered and were consistent with controls in the recovery phase.
- No visible ophthalmic lesions were noted in the study.
- Slightly lower (statistically significant) mean motor activity was noted in males at 10 mg/kg and at 2 mg/kg with no dose-response trend.
- Microscopic findings in many tissues were consistent with the known effects of MMAE on inducing mitotic arrest (due to inhibition of tubulin formation), particularly in cells/tissues with a higher background mitotic rate.
- At ≥6 mg/kg microscopic findings included decreased cellularity in bone marrow characterized by decreases in red cell mass, reticulocyte count, and absolute neutrophil count in the peripheral blood; decreased cortical cellularity and increased apoptosis/mitoses in thymus correlated with decrease of lymphocytes; liver toxicity characterized by effects on serum liver transaminases, total bilirubin, and microscopically by increased apoptosis/mitoses of hepatocytes, sinusoidal cells (endothelial and Kupffer cells), and bile duct epithelium and multifocal hepatic necrosis; skin effects consisted of a minimal increase in apoptosis/atrophy of the adnexa epithelial cells (sebaceous gland/hair follicle) and a minimal increase in mitoses in the epidermis and, increased apoptosis/mitoses (minimal to slight severity) in the epididymis duct, These findings exhibited reversibility after a 6-week recovery period.
- At ≥ 2 mg/kg microscopic findings in the lung consisted of a macrophage infiltrate in the alveolus and hyperplasia/hypertrophy of Type 2 pneumocytes of males administered 10 mg/kg; testes toxicity was characterized seminiferous tubule degeneration with consequent abnormal lumen contents in the epididymis. This toxicity did not reverse at the end of the 6-week recovery.

Table 8: Microscopic Findings at Terminal Necropsy in Rats

	DCDS4501A (mg/kg)							
Sex	Males				Females			
Dose Level	0	2[b]	6	10[b]	0	2	6	10
Marrow, Femur								
Number Examined	10	11	10	11	10	10	10	10
Cellularity, Decreased	0	0	10 (2.4)	11 (4.0)	0	0	3 (1.0)	10 (1.5)
Marrow, Sternum								
Number Examined	10	11	10	11	10	10	10	10
Cellularity, Decreased	0	0	9 (1.6)	11 (3.8)	0	0	4 (1.3)	9 (1.8)
Thymus								
Number Examined	10	11	10	11	10	10	10	10
Cellularity, Decreased, Cortex	0	0	9 (1.2)	11 (3.5)	0	0	10 (1.8)	10 (3.2)
Apoptosis/Mitoses, Increased	0	0	10 (1.5)	11 (2.1)	0	0	10 (1.5)	10 (2.2)
Lymph Node, Mandibular								
Number Examined	10	11	10	11	10	10	10	10
Mitoses, Increased, Med./Paracortex	0	3 (1.0)	7 (1.0)	9 (1.0)	0	2 (1.0)	9 (1.0)	8 (1.0)
Pancreas								
Number Examined	10	11	10	11	10	10	10	10
Apoptosis/Mitoses, Acinar Cells, Increased	3 (1.0)	2 (1.0)	6 (1.2)	6 (1.3)	2 (1.0)	1 (1.0)	4 (1.0)	4 (1.5)
Eye								
Number Examined	10	11	10	11	10	10	10	10
Mitoses, Increased, Cornea	0	0	2 (1.0)	4 (1.0)	0	0	1 (1.0)	5 (1.0)
Duodenum								
Number Examined	10	11	10	11	10	10	10	10
Apoptosis/Mitoses, Increased	0	0	6 (1.0)	10 (1.0)	0	0	4 (1.0)	6 (1.0)
Jejunum								
Number Examined	10	11	10	11	10	10	10	10
Apoptosis/Mitoses, Increased	0	0	9 (1.0)	10 (1.0)	0	0	6 (1.0)	8 (1.0)
Ileum								
Number Examined	10	11	10	11	10	10	10	10
Apoptosis/Mitoses, Increased	0	0	7 (1.0)	9 (1.0)	0	0	5 (1.0)	6 (1.0)

a Incidence and mean severity (number in parentheses) are based on the number of animals with finding.
b Groups 2 and 4 each include findings, as appropriate, from one male scheduled for recovery necropsy that died on Study Day 2 and one male euthanized in moribund condition on Study Day 31 (Recovery Day 6), respectively.

	DCDS4501A (mg/kg)							
Sex	Males				Females			
Dose Level	0	2	6	10	0	2	6	10
Testis								
Number Examined	5	4	5	4	NA	NA	NA	NA
Atrophy	0	4 (2.3)	5 (4.6)	4 (5.0)				
Epididymis								
Number Examined	5	4	5	4	NA	NA	NA	NA
Abnormal Contents, Lumen	0	3 (2.3)	5 (4.0)	4 (4.0)				
Lung								
Number Examined	5	4	5	4	5	5	5	5
Infiltrates, Macrophages Alveolus	0	0	0	1 (1.0)	0	0	0	0
Liver								
Number Examined	5	4	5	4	5	5	5	5
Necrosis, Random, Focal	0	0	0	0	0	0	0	1 (2.0)

NA = Not applicable.
a Incidence and mean severity (number in parentheses) are based on the number of animals with finding.

Table 8 (Continued): Microscopic Findings at Terminal Necropsy in Rats

	DCDS4501A (mg/kg)							
Sex	Males				Females			
Dose Level	0	2	6	10	0	2	6	10
Testis								
Number Examined	5	4	5	4	NA	NA	NA	NA
Atrophy	0	4 (2.3)	5 (4.6)	4 (5.0)				
Epididymis								
Number Examined	5	4	5	4	NA	NA	NA	NA
Abnormal Contents, Lumen	0	3 (2.3)	5 (4.0)	4 (4.0)				
Lung								
Number Examined	5	4	5	4	5	5	5	5
Infiltrates, Macrophages Alveolus	0	0	0	1 (1.0)	0	0	0	0
Liver								
Number Examined	5	4	5	4	5	5	5	5
Necrosis, Random, Focal	0	0	0	0	0	0	0	1 (2.0)

NA = Not applicable.
a Incidence and mean severity (number in parentheses) are based on the number of animals with finding.

	DCDS4501A (mg/kg)							
Sex	Males				Females			
Dose Level	0	2[b]	6	10[b]	0	2	6	10
Intravenous Site								
Number Examined	10	10	10	11	10	10	10	10
Apoptosis/Mitoses/Atrophy, Epithelium, Adnexa	0	6 (1.0)	10 (1.3)	11 (1.4)	0	5 (1.0)	9 (1.3)	10 (1.4)
Apoptosis/Mitoses, Increased, Epidermis	0	2 (1.0)	7 (1.1)	11 (1.5)	0	1 (1.0)	8 (1.4)	10 (1.5)
Lung								
Number Examined	10	11	10	11	10	10	10	10
Infiltrates, Macrophages Alveolus	0	1 (2.0)	1 (1.0)	8 (1.1)	0	2 (1.0)	1 (1.0)	2 (1.0)
Hyperplasia/Hypertrophy, Type-2 Pneumocyte	0	0	0	3 (1.7)	0	0	0	0
Uterus								
Number Examined	NA	NA	NA	NA	10	10	10	10
Mitoses, Increased					0	0	0	3 (1.0)
Mammary, Male								
Number Examined	9	11	10	10	NA	NA	NA	NA
Atrophy, Duct/ Alveolus[c]	0	1	9	10				
Mitoses, Increased, Duct Epithelium	0	0	8 (1.1)	7 (1.0)				
Testis								
Number Examined	10	11	10	11	NA	NA	NA	NA
Degeneration, Seminiferous tubules	0	8 (1.1)	10 (2.6)	11 (4.2)				
Apoptosis, Increased	0	11 (1.5)	10 (1.0)	11 (1.5)				
Epididymis								
Number Examined	10	11	10	11	NA	NA	NA	NA
Abnormal Contents, Lumen	0	8 (1.3)	10 (2.8)	11 (4.0)				
Apoptosis/Mitoses, Increased Duct Epithelium	0	0	10 (1.0)	10 (1.4)				
Infiltrate, Lymphocytes	0	2 (1.0)	10 (1.1)	11 (1.4)				

NA = Not applicable.
a Incidence and mean severity (number in parentheses) are based on the number of animals with finding.
b Groups 2 and 4 each include findings from one male scheduled for recovery necropsy that died on Study Day 2 and one male euthanized in moribund condition on Study Day 31 (Recovery Day 6), respectively.
c Finding of Atrophy, Duct/Alveolus recorded as present.

Table 9: Microscopic Findings at Recovery Necropsy in Rats

	DCDS4501A (mg/kg)							
Sex	Males				Females			
Dose Level	0	2	6	10	0	2	6	10
Testis								
Number Examined	5	4	5	4	NA	NA	NA	NA
Atrophy	0	4 (2.3)	5 (4.6)	4 (5.0)				
Epididymis								
Number Examined	5	4	5	4	NA	NA	NA	NA
Abnormal Contents, Lumen	0	3 (2.3)	5 (4.0)	4 (4.0)				
Lung								
Number Examined	5	4	5	4	5	5	5	5
Infiltrates, Macrophages Alveolus	0	0	0	1 (1.0)	0	0	0	0
Liver								
Number Examined	5	4	5	4	5	5	5	5
Necrosis, Random, Focal	0	0	0	0	0	0	0	1 (2.0)

NA = Not applicable.
a Incidence and mean severity (number in parentheses) are based on the number of animals with finding.

	DCDS4501A (mg/kg)							
Sex	Males				Females			
Dose Level	0	2[b]	6	10[b]	0	2	6	10
Cecum								
Number Examined	10	11	10	11	10	10	10	10
Apoptosis/Mitoses, Increased	0	0	1 (1.0)	4 (1.0)	0	0	0	3 (1.0)
Rectum								
Number Examined	10	11	10	11	10	10	10	10
Apoptosis/Mitoses, Increased	0	0	3 (1.0)	5 (1.0)	0	0	4 (1.0)	7 (1.0)
Heart								
Number Examined	10	11	10	11	10	10	10	10
Mitoses, Increased, Atrium	0	0	0	4 (1.0)	0	0	0	2 (1.0)
Spleen								
Number Examined	10	11	10	10	10	10	10	10
Mitoses, Increased, Red Pulp	0	0	0	6 (1.0)	0	0	0	3 (1.0)
Pituitary								
Number Examined	10	11	10	11	10	10	10	10
Apoptosis/Mitoses, Increased	0	2 (1.0)	3 (1.0)	8 (1.4)	0	2 (1.0)	3 (1.0)	9 (1.1)
Harderian Gland								
Number Examined	10	11	10	11	10	10	10	10
Apoptosis, Increased, Acinar Cells	0	0	1 (1.0)	1 (1.0)	0	0	1 (1.0)	2 (1.0)
Liver								
Number Examined	10	11	10	11	10	10	10	10
Necrosis, Random, Focal	0	0	0	3 (2.0)	1 (2.0)	0	2 (1.5)	3 (2.0)
Apoptosis/Mitoses, Increased	0	0	4 (1.0)	7(1.1)	0	0	6(1.0)	7(1.1)
Skin/Subcutis								
Number Examined	10	11	10	11	10	10	10	10
Apoptosis/Atrophy, Epithelium, Adnexa	0	0	7 (1.0)	11 (1.0)	0	0	10 (1.0)	10 (1.1)
Mitoses, Increased, Epidermis	0	0	3 (1.0)	11 (1.0)	0	0	6 (1.0)	7 (1.0)
Erosion/Ulcer	0	0	0	1 (3.0)	0	0	1 (1.0)	1 (1.0)

a Incidence and mean severity (number in parentheses) are based on the number of animals with finding.
b Groups 2 and 4 each include findings, as appropriate, from one male scheduled for recovery necropsy that died on Study Day 2 and one male euthanized in moribund condition on Study Day 31 (Recovery Day 6), respectively.

Table 10: Toxicokinetics for Polatuzumab Vedotin and MMAE in Rat Serum

Dose (mg/kg):	2		6		10	
No. of animals	M: 9	F: 9	M: 9	F: 9	M: 9	F: 9
Toxicokinetics: Total Antibody						
AUC (day • µg/mL)						
Study Day 1: $AUC_{0–7}$ (day • µg/mL)	132	97.8	534	293	658	594
Study Day 22: $AUC_{21–28}$ (day • µg/mL)	177	122	586	500	923	923
Study Day 22: $AUC_{21–last}$ (day • µg/mL)	418	257	1050	945	1690	1510
Cmax (µg/mL)						
Study Day 1	67.8	58.1	260	216	406	298
Study Day 22	81.3	80.6	258	174	392	393
Toxicokinetics: MMAE						
AUC (day • µg/mL)						
Study Day 1: $AUC_{0–4}$ (day • µg/mL)	a	a	0.498	0.382	0.976	0.717
Study Day 22: $AUC_{21–25}$ (day • µg/mL)	a	a	0.703	0.450	1.33	0.979
Cmax (µg/mL)						
Study Day 1	a	a	0.169	0.136	0.367	0.253
Study Day 22	a	a	0.216	0.157	0.457	0.323

[a]*TK parameters for animals given 2 mg/kg were below the limit of quantitation.*

Study title: Multiple Dose Intravenous Toxicity, Toxicokinetic, and Cardiovascular Safety Pharmacology Study of DCDS4501A and DCDS5017A Administered Intravenously to Cynomolgus Monkeys Once Every 3 Weeks for Four Doses, Followed by at Least a 9-Week Recovery Period

Study no.: 10-0044
Study report location: 4.2.3.2.
Conducting laboratory and location: (b) (4)

Date of study initiation: 10 Mar 2010
GLP compliance: Yes
QA statement: Yes
Drugs, lot #s, and % purity:
1. DCDS4501A (clinical candidate), 807001, (b) (4) (nominal); (b) (4) (b) (4) (actual), DAR: 3.7.
2. DCDS5017A (surrogate), 815164, (b) (4) (b) (4) (nominal); (b) (4) (actual), DAR:3.5

Key Study Findings

- DCDS4501A (clinical candidate) and DCDS5017A (surrogate) resulted in comparable toxicities. Toxicities included hypocellularity of the bone marrow with corresponding myelosuppression at 3 and 5 mg/kg.

- DCDS5017A at 3 and 5 mg/kg induced decreases in circulating B-lymphocytes and depletion of lymphoid follicular germinal centers in the spleen in all animals.
- Anti-therapeutic antibodies (ATA) were detected in several animals given DCDS4501A and DCDS5017A but did not impact the exposure.

Methods

Doses:	Vehicle, 1, 3, and 5 mg/kg DCDS4501A (clinical candidate); 3 and 5 mg/kg DCDS5017A (surrogate ADC)
Frequency of dosing:	Once every 3 weeks (days 1, 22, 43, 64).
Route of administration:	Bolus intravenous (IV) injection
Dose volume:	
Formulation/Vehicle:	DCDS4501A vehicle ((b) (4) histidine acetate, pH 5.5, (b) (4) sucrose, (b) (4) polysorbate 20). Note: this vehicle was used as a diluent for both test articles, DCDS4501A and DCDS5017A
Species/Strain:	Cynomolgus monkey
Number/Sex/Group:	5/sex/group (2/sex used for recovery)
Age:	3.0-3.7 yr for males, 2.8-3.83 yr for females
Weight:	Males 2.3 kg to 3.7 kg Females 2.1 kg to 3.3 kg
Deviation from study protocol:	None that impact the study outcome

Observations and Results

Parameters	Major findings
Mortality	One male treated with high dose DCDS5017A died on Day 53 prior to moribund humane sacrifice. The clinical signs included decreased activity, hunched appearance, and poor coordination. Cause of death was bacterial endocarditis with corresponding material accumulation on inner surface of right ventricle and red or white pinpoint foci on the lungs. Bacteria or signs of bacterial infection where seen in other organs. Bacterial infection was likely secondary to myelosuppression due to study drug. One female treated with high dose DCDS4501A was moribund and sacrificed on Day 55. Clinical pathology findings included increased neutrophil count, and decreased lymphocyte and eosinophil counts, and minimally decreased indicators of RBC mass (Hb, Hct, and RBC count). Coagulation changes included decreased albumin and increased globulin and fibrinogen with no macroscopic or microscopic evidence of thrombosis.
Clinical Signs	Unremarkable
Body Weights	Unremarkable
Respiration Rates (respiration rates and pulse oximetry)	Unremarkable
Ophthalmoscopy	Unremarkable
ECG (including blood pressure, heart rates, and ECGs)	Unremarkable
Neurological	Reduced patellar reflexes over weeks 2 and 10 with no dose response:

<table>
<tr><td></td><td>DCDS4501A:
1 mg/kg -1 male and 1 female
3 mg/kg - 3 females
5 mg/kg -1 female
DCDS5017A
3 mg/kg - 1 male and 1 female
5 mg/kg - 6 females.</td></tr>
<tr><td>Hematology</td><td>Both DCDS4501A and DCDS5017A had similar hematologic findings that were consistent with bone marrow toxicity and associated peripheral blood cell effects due to suppression of myeloid and erythroid cells, attributable to the pharmacologic activity of monomethyl auristatin E (MMAE).

<table>
<tr><td>Drug</td><td colspan="3">DCDS4501A</td><td colspan="2">DCDS5017A</td></tr>
<tr><td>Dose mg/kg</td><td>1</td><td>3</td><td>5</td><td>3</td><td>5</td></tr>
<tr><td>Reticulocytes (day 8)</td><td>-9</td><td>-37</td><td>-50</td><td>-33</td><td>-71</td></tr>
<tr><td>Reticulocytes (day 71)</td><td>-</td><td>-45</td><td>-49</td><td>-52</td><td>-48</td></tr>
<tr><td>Lymphocytes (day 8)</td><td>-26</td><td>-25</td><td>-54</td><td>-65</td><td>-50</td></tr>
<tr><td>Lymphocytes (day 71)</td><td>-17</td><td>-29</td><td>-42</td><td>-52</td><td>-57</td></tr>
<tr><td>Neutrophils (day 8)</td><td>-9</td><td>-21</td><td>-30</td><td>-57</td><td>-78</td></tr>
<tr><td>Monocytes (day 8)</td><td>-</td><td>-</td><td>-38</td><td>-26</td><td>-64</td></tr>
</table>
Values in table represent percent change from control mean values (pooled sexes). '–' no change or not toxicologically relevant.

Findings were reversible.

Flow cytometry analysis showed decreases in B-lymphocytes (CD20+) up to 79% and 84% in 3 and 5 mg/kg DCDS5017A groups, respectively, consistent with pharmacodynamic activity.</td></tr>
<tr><td>Clinical Chemistry</td><td>Globulins were decreased ~25% (pooled sexes) during the main study period in DCDS5017A and albumin:globulin ratios were correspondingly higher.
Globulins were still decreased 24% by the end of recovery.</td></tr>
<tr><td>Anti-drug antibodies</td><td>Anti-drug antibodies were found in 43% and 20% of DCDS4501 and DCDS5017A-treated animals, respectively.
DCDS4501A:
1 mg/kg: 5/10
3 mg/kg: 5/10
5 mg/kg: 3/10
DCDS5017A
3 mg/kg: 3/10
5 mg/kg: 1/10</td></tr>
<tr><td>Urinalysis</td><td>Unremarkable</td></tr>
<tr><td>Gross Pathology</td><td>Unremarkable</td></tr>
<tr><td>Organ Weights</td><td>Unremarkable</td></tr>
<tr><td>Histopathology
Adequate battery: Yes</td><td>The lymphoid follicular germinal centers in the spleen were absent in all DCDS5017A-treated animals. Recovery sacrifice findings were unremarkable.
<table>
<tr><td></td><td colspan="6">Males</td><td colspan="6">Females</td></tr>
<tr><td>Dose mg/kg</td><td>0</td><td>1[a]</td><td>3[a]</td><td>5[a]</td><td>3[b]</td><td>5[b]</td><td>0</td><td>1[a]</td><td>3[a]</td><td>5[a]</td><td>3[b]</td><td>5[b]</td></tr>
<tr><td># of Animals</td><td>3</td><td>3</td><td>3</td><td>3</td><td>3</td><td>2</td><td>3</td><td>3</td><td>3</td><td>3</td><td>3</td><td>3</td></tr>
<tr><td colspan="13">BONE MARROW, STERNUM</td></tr>
<tr><td colspan="13">Hypocellularity</td></tr>
<tr><td>mild</td><td>0</td><td>0</td><td>2</td><td>1</td><td>1</td><td>0</td><td>0</td><td>0</td><td>0</td><td>1</td><td>2</td><td>2</td></tr>
</table></td></tr>
</table>

	moderate 0 0 0 1 0 0 0 0 0 0 0 0 Hypercellularity Myeloid mild 0 0 1 1 2 2 0 0 3 2 1 1 [a] DCDS4501A; [b] DCDS5017A; values in the table represent the incidence of findings in each group.
Toxicokinetics	Serum and plasma samples were collected and assayed for total antibody and unconjugated MMAE concentrations, respectively. See tables below.
Polatuzumab Vedotin and Surrogate ADC	Total antibody exposure increased in proportion with the increase in polatuzumab vedotin dose level from 1 to 5 mg/kg and in surrogate ADC dose level from 3 to 5 mg/kg. No accumulation was observed after multiple doses of polatuzumab vedotin, whereas the accumulation ratio (AUC_{63-84}/AUC_{0-21}) for the surrogate ADC ranged from 1.22 to 1.52. Summary of Toxicokinetic Parameters for Polatuzumab Vedotin and Surrogate ADC in Monkey Serum (combined for males and females)
MMAE	The toxicokinetic parameters for MMAE were similar between polatuzumab vedotin (clinical) and surrogate ADC. **Summary of Toxicokinetic Parameters of Free MMAE (Clinical ADC) and Free MMAE (Surrogate ADC) in Cynomolgus Monkey Plasma (combined for males and females)**

		First Dose		Last Dose	
Dose Level mg/kg [a] (μg/m2) [b]	Test Material	C_{max} (μg/mL)	$AUC_{(0–21)}$ (μg • day/mL)	C_{max} (μg/mL)	$AUC_{(63–84)}$ (μg • day/mL)
1 (~220)	Polatuzumab vedotin	34.0	138	27.6	138
3 (~659)	Polatuzumab vedotin	90.6	440	101	485
5 (~1098)	Polatuzumab vedotin	157	744	177	796
3 (~622)	Surrogate ADC	76.7	216	89.4	295
5 (~1038)	Surrogate ADC	140	404	147	523

~ = approximately; AUC0–21 = TK Day 0 to TK Day 21 AUC63–84 = TK Day 63 to TK Day 84.
a Dose expressed as mg total surrogate ADC/kg of body weight.
b Dose of surrogate ADC expressed as dose of MMAE (μg/m2).

Day 64

Group No.	Dose Level mg/kg (μg/m^2)	Test Material		Tmax (day)	Cmax (ng/mL)	AUC(0-t) (ng•day/mL)	AUC(0-3) (ng•day/mL)	Cmax/D*	AUC(0-t)/D*	AUC(0-3)/D*
3	3 (~659) [a]	Clinical	Mean [c]	3	0.0726	0.394	0.181	0.000110	0.000599	0.000274
			SD		0.00910	0.107	0.0174	0.0000138	0.000163	0.0000263
4	5 (~1098) [a]	Clinical	Mean [c]	3	0.104	0.565	0.253	0.0000943	0.000515	0.000231
			SD		0.0213	0.0984	0.0484	0.0000194	0.0000896	0.0000441
5	3 (~622) [b]	Surrogate	Mean [c]	3	0.0729	0.381	0.178	0.000117	0.000612	0.000286
			SD		0.00814	0.102	0.0264	0.0000131	0.000164	0.0000425
6	5 (~1038) [b]	Surrogate	Mean [c]	3	0.107	0.583	0.263	0.000103	0.000561	0.000254
			SD		0.0218	0.105	0.0518	0.0000210	0.000101	0.0000499

a Dose expressed as mg total DCDS4501A /kg of body weight (dose of DCDS4501A expressed as dose of MMAE (μg/m2)).
b Dose expressed as mg total DCDS5017A /kg of body weight (dose of DCDS5017A expressed as dose of MMAE (μg/m2)).
c Median value reported for Tmax.
* Dose level in μg/m^2 was used in calculations.

Additional toxicology studies

Toxicities of MMAE were assessed in repeat-dose studies in rats (Study no. 7646-118) and monkeys (Study no. SNBL.163.16), which are summarized below.

Sprague-Dawley rats 15/sex) were given IV doses of 0.0097, 0.097, and 0.194 mg/kg weekly (QW) for a total of 4 doses with a 4-week recovery period. Animals were sacrificed on Day 26 for dosing phase.

Rats

- Decreases in RBC parameters (markedly reduced absolute reticulocyte count up to 94%, hemoglobin concentration up to 36% lower than control), and increased gamma-glutamyl transferase (GGT), total bilirubin and aspartate aminotransferase (AST).
- Minimal to marked lymphoid depletion of the thymus and bone marrow hypocellularity, liver toxicity was characterized microscopically by increased incidence of hepatocellular necrosis, testicular changes included irreversible diffuse seminiferous tubular degeneration, and decreased spermatocytes with consequent epididymis aspermia.
- At recovery, no thymic, bone marrow, or liver findings were noted, indicating complete reversibility with the exception of findings in male reproductive system. Testicular changes consisting of diffuse seminiferous tubular degeneration, Sertoli cell vacuolation, and reduced spermatogenesis and epididymal aspermia were observed at high-dose (0.194 mg/kg).

Monkeys (5M/5F) were given IV doses 0.058 mg/kg every 3 weeks (Q3W) for a total of 4 doses (Days 1, 22, 43, and 64) followed by a 5-week recovery period. Animals were sacrificed on Day 71 (7 days after the last dose).

<u>Monkeys</u>

- Decreases in RBC parameters and WBCs.
- Bone marrow hypocellularity and decrease in lymphocytes in the thymus and spleen, which was associated with decreased thymus and splenic organ weights.

7 Genetic Toxicology

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

Study title: Bacterial Reverse Mutation Assay

Study no.:	AA66EH.503.BTL
Study report location:	4.2.3.3.1.
Conducting laboratory and location:	(b) (4)
Date of study initiation:	03 October 2002
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	SGD-001010, -0-01, 98.7%

Key Study Findings

- SGD-001010 (MMAE or SGD-1010) was not cytotoxic (growth inhibition) to the test system up to 5000 µg/plate.
- SGD-001010 was negative in bacterial reverse mutation test with or without metabolic activation up to 5000 µg/plate.

Methods

Strains:	*Salmonella typhimurium* (TA98, TA100, TA1535, and TA1537) and *Escherichia coli* WP2uvrA
Concentrations in definitive study:	75, 200, 600, 1800 and 5000 µg per plate
Basis of concentration selection:	Neither precipitate nor toxicity were observed in the initial toxicity-mutation assay
Negative control:	DMSO
Positive control:	-S9: Sodium azide for TA1535, TA100 9-aminoacridine for TA1537 2-Nitrofluorene for TA98 Methyl methanesulfonate for WP2 uvrA +S9:2-Aminoanthracene for all strains
Formulation/Vehicle:	DMSO
Incubation & sampling time:	Plate incorporation method: 48 to 72 hours at 37±2°C.

Study Validity

- Selection of the tester strains was adequate based upon Guideline for Industry: Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals (ICHS2A, April 1996).
- A minimum of three non-toxic doses were included for each strain.

- Tester strain culture titers were greater than or equal to $0.3x10^9$ cells/mL.
- The vehicle control values were within the laboratory historical ranges.
- The positive control compounds (± S9 mix) produced increases in the number of revertant colonies (at least 3x increase in the number of revertants over the mean value of the respective negative control).

Results

- No positive mutagenic responses were observed with any of the tester strains in either the presence or absence of S9 activation.

7.2 *In Vitro* Assays in Mammalian Cells

Study title: L5178Y TK+/- Mouse Lymphoma Forward Mutation Assay with a Confirmatory Assay

Study no.:	8204155
Study report location:	4.2.2.3.1.
Conducting laboratory and location:	(b) (4)
Date of study initiation:	20 April 2009
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	SGD-1010, 2002E, 92.8%

Key Study Findings

- SGD-1010 (MMAE) was cytotoxic and was negative in the L5178Y TK+/- mouse lymphoma forward mutation assay.

Methods

Cell line:	Mouse lymphoma L5178Y cell line,
Concentrations in definitive study:	4-hour treatment with S9: 0.05, 0.1, 0.25, 0.5, 1.0, 2.5, 5, 10, 20, 30, 40, 50, 60, and 70 ng/mL. 4-hour treatment without S9: 0.005, 0.01, 0.05, 0.1, 0.25, 0.5, 0.75, 1, 2.5, 5, 7.5, 10, 12.5, and 15 ng/mL. 24-hour treatment without S9: 0.001, 0.005, 0.01, 0.05, 0.1, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, and 6 ng/mL.
Basis of concentration selection:	Cytotoxicity (decreases in relative suspension growth)
Negative control:	0.01N HCl/0.9% saline
Positive control:	With S9: Methylcholanthrene Without S9: Methyl methanesulfonate
Formulation/Vehicle:	0.01N HCl/0.9% saline

Incubation & sampling time: 4-hour treatment with and without S9, and a 24-hour treatment without S9.

Study Validity

The study validity was evaluated using criteria recommended by the Mouse Lymphoma Assay Workgroup of the International Workshop on Genotoxicity testing for assay acceptance criteria, positive controls and data evaluation (Moore *et al*., 2006, 2007). All criteria for a valid assay were met.

Results:

- SGD-1010 (MMAE) was cytotoxic (decreases in relative total growth, RTG) to the test system under all three (4-hour treatment with and without S9, and a 24-hour treatment without S9) treatment conditions.
- SGD-1010 (MMAE) was negative in the L5178Y TK+/- mouse lymphoma forward mutation assay with a confirmatory assay up to 10 to 20% RTG.

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

Study title: *In Vivo* Rat Bone Marrow Micronucleus Assay

Study no:	8204151
Study report location:	4.2.3.3.2.
Conducting laboratory and location:	(b) (4)
Date of study initiation:	28 April 2009
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	SGD-1010 (MMAE), 2002E, 92.8%

Key Study Findings

- SGD-1010 was positive in the rat bone marrow micronucleus assay.
- SGD-1010 induced micronuclei via an aneugenic mode of action based on 60-76% positive micronuclei for kinetochore staining.

Methods

Doses in definitive study:	0, 0.01, 0.1, and 0.2 mg/kg
Frequency of dosing:	Once
Route of administration:	IV injection
Dose volume:	5
Formulation/Vehicle:	3.9% 0.01N Hydrochloric Acid/96.1% 0.9% Sodium Chloride for Injection, USP (HCl/Saline)
Species/Strain:	CD® (SD) rats
Number/Sex/Group:	5 males/group/timepoint
Basis of dose selection:	0.2 mg/kg was estimated to the MTD based on prior general toxicity studies.
Negative control:	(HCl/Saline)
Positive control:	Cyclophosphamide, 60 mg/kg Carbendazim, 1250 and 1500 mg/kg/day

Study Validity

- The vehicle control group mean micronucleated polychromatic erythrocytes (PCEs) was within the historical control range.
- A statistically significant elevation of the mean micronucleated PCEs of the positive control relative to the vehicle control was observed and was within the historical positive control data.

Results

- SGD-1010 was cytotoxic to bone marrow (ratio PCE/NCE) tested up to 0.2 mg/kg (estimated MTD).
- SGD-1010 was positive for the induction of increased micronucleated PCE at 0.1 and 0.2 mg/kg MMAE at 24 hours harvest time and at 0.2 mg/kg at 48-hour harvest time.
- SGD-1010 was positive for centromere containing micronuclei compared to vehicle control (HCl/saline).
- The centromere+ micronuclei were 16-28% in cyclophosphamide clastogenic control, 68% in carbendazim aneugenic control, and 60-76% in SGD-1010-treated animals.

7.4 Other Genetic Toxicity Studies

None

8 Carcinogenicity

No carcinogenicity studies were submitted.

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

No fertility and early embryonic development studies were submitted.

9.2 Embryonic Fetal Development

Dedicated embryo-fetal developmental toxicity studies were not conducted with polatuzumab vedotin. However, MMAE (SGD-1010) was evaluated in rats in a GLP embryo-fetal developmental and TK study (Study 8204397) to determine maternal and embryo-fetal toxicity and teratogenic potential.

Study title: Intravenous Injection Study for Effects on Embryofetal Developmental and Toxicokinetics with SGN-35 and SGD-1010 in Rats

Study no.:	8204397
Study report location:	4.2.3.5.2.
Conducting laboratory and location:	(b) (4)
Date of study initiation:	09 September 2009
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	SGD-1010 (MMAE); lot#, 2002E, purity: 95.8% (HPLC)

Key Study Findings

- Clinical observations of pale appearance and red/black vaginal discharge was observed in dams.
- Decreases in RBC parameters were noted similar to previous MMAE toxicity studies in rats.
- Administration of SGD-1010 to pregnant rats resulted in teratogenic and embryo-fetal adverse toxicity.
- SGD-1010 crossed the placenta.

Methods

Doses:	0, 0.2 mg/kg SGD-1010
Frequency of dosing:	Twice: once each on GD 6 and GD 13
Dose volume:	5 ml/kg
Route of administration:	Intravenous injection
Formulation/Vehicle:	3.9% 0.01 N hydrochloric acid/ 96.1% 0.9% sodium chloride for injection (HCl/saline).
Species/Strain:	Rat/Crl:CD(SD)
Number/Sex/Group:	Mated females (25 for main and 9 for TK)
Study Design:	Cesarean section was performed on GD 21: gross observations, uterine contents and weights, live/dead fetuses, early/late resorptions, abnormalities, number of corpora lutea. Fetal examinations: gender, body weights, external abnormalities; half of the fetuses from each litter were processed for visceral examination. The remaining fetuses were

processed for skeletal examination.

Deviation from study protocol: None that impacted the outcome of the study

Observations and Results

<table>
<tr><td>Parameters</td><td>Major findings</td></tr>
<tr><td>Mortality</td><td>All animals survived until scheduled sacrifice except one dam in the SGD-1010 group, who delivered on GD 21 and was sacrificed.</td></tr>
<tr><td>Clinical Signs</td><td>SGD-1010-related paleness (both ears and entire body), red/black vaginal discharge, and red fluid in cage pan were noted.</td></tr>
<tr><td>Body Weights</td><td>SGD-1010-related decrease in mean maternal body weight change of 20% was noted during the study period GD 6 through GD 21 compared to controls.</td></tr>
<tr><td>Food Consumption</td><td>Food consumption decreased by 12% from GD 6 through 21.</td></tr>
<tr><td>Hematology</td><td>Percent changes in the SGD1010 compared to mean control
<table>
<tr><td>mg/kg</td><td>RBC</td><td>HGB</td><td>HCT</td><td>WBC</td><td>NEUT</td><td>EOS</td><td>LUC</td><td>PRET</td></tr>
<tr><td>0</td><td>6.29</td><td>12.2</td><td>34.7</td><td>10.74</td><td>3.83</td><td>0.1</td><td>0.09</td><td>2.8</td></tr>
<tr><td>0.2</td><td>-35</td><td>-31</td><td>-29</td><td>-19</td><td>-41</td><td>-70</td><td>44</td><td>396</td></tr>
</table></td></tr>
<tr><td>Fetal Weights (g) covariate adjusted</td><td>There was no significant change in the SGD-1010 treated group mean total (M and F) fetal body weights compared to control (-4% change).</td></tr>
<tr><td>Necropsy findings</td><td>Summary Cesarean Section Data
<table>
<tr><td>Treatments</td><td>Control</td><td>SGD-1010</td></tr>
<tr><td>Dose mg/kg</td><td>0</td><td>0.2</td></tr>
<tr><td>Gravid Uterine weights (g) (mean)</td><td>97.73</td><td>74.2</td></tr>
<tr><td>Females Mated (N)</td><td>25</td><td>25</td></tr>
<tr><td>Pregnant (N)</td><td>25</td><td>24</td></tr>
<tr><td>Aborted (N)</td><td>0</td><td>0</td></tr>
<tr><td>Died (N)</td><td>0</td><td>0</td></tr>
<tr><td>Delivered Early (N) [NL]</td><td>0</td><td>1</td></tr>
<tr><td>Pregnant at C-section (N)</td><td>25</td><td>24</td></tr>
<tr><td>Dams with Viable Fetuses (N)</td><td>25</td><td>23</td></tr>
<tr><td>Dams with no Viable Fetuses (N)</td><td>0</td><td>1</td></tr>
<tr><td>Corpora Lutea (mean)</td><td>13.8</td><td>14.2</td></tr>
<tr><td>Implantation Sites (mean)</td><td>12.8</td><td>12.8</td></tr>
<tr><td>Preimplantation Loss (mean%)</td><td>6.8</td><td>9.3*</td></tr>
<tr><td>Resorptions:</td><td></td><td></td></tr>
<tr><td>Total (mean%)</td><td>1</td><td>27.4*</td></tr>
<tr><td>Early (mean%)</td><td>1</td><td>22.2*</td></tr>
<tr><td>Late (mean%)</td><td>0</td><td>5.2*</td></tr>
<tr><td>Dead Fetuses Total</td><td>0</td><td>0</td></tr>
<tr><td>Post implantation Loss (mean%)</td><td>1</td><td>27.4*</td></tr>
<tr><td>Live Fetuses (mean%)</td><td>99</td><td>72.6</td></tr>
<tr><td>% Male fetuses</td><td>52.2</td><td>50</td></tr>
<tr><td>Mean fetal weights (grams, M+F)</td><td>5.62</td><td>5.4</td></tr>
</table>
* values are outside of the Historical Control (HC) Range</td></tr>
</table>

C-section data includes data from litters with no viable fetuses

Offspring (Malformations, Variations)

Summary of Fetal External Findings

Treatments	Control	SGD-1010
Dose mg/kg	0	0.2
Litters Evaluated	25	23
Fetuses Evaluated	317	220
Live	317	220
Dead	0	0
Variations		
Curly Tail [N (%)][NL]	F 0 (0) L 0 (0)	F 1 (0.5) L 1 (4.3)
Malformations		
Protruding Tongue [N (%)]	F 0 (0) L 0 (0)	F 1 (0.5)* L 1 (4.3)*
Malrotated Hindlimbs [N (%)]	F 0 (0) L 0 (0)	F 2 (0.9)* L 2 (8.7)*
Gastroschisis [N (%)]	F 0 (0) L 0 (0)	F 2 (0.9)* L 2 (8.7)*
Agnathia [N (%)]	F 0 (0) L 0 (0)	L 1 (0.5)* F 1 (4.3)*
Summary of Fetal Skeletal Findings		
Litters Evaluated	25	23
Fetuses Evaluated	161	112
Variations		
Less Than Four Metatarsals Ossified [N (%)][NL]	F 0 (0) L 0 (0	F 1 (0.9) L 1 (4.3)
Malformations		
Mandible(s) Malformed (corresponds to agnathia) [N (%)]	F 0 (0) L 0 (0	F 1 (0.9)* L 1 (4.3)*
Split Sternebra(e) [N (%)][NL]	F 0 (0) L 0 (0	F 1 (0.9) L 1 (4.3)
Shortened Long Bones(s) [N (%)]	F 0 (0) L 0 (0	F 1 (0.9)* L 1 (4.3)*

F: fetus; L: litter.

* values are outside Historical Control (HC) Range of the CRO (b) (4) (b) (4) HC Ranges from 2008-2010

NL=not listed; no available HC data for this finding

Following bolus IV administration of SGD-1010 at 0.2 mg/kg, serum concentrations of SGD-1010 were approximately 60% higher on GD 13 than on GD 6. Maternal exposure of MMAE was measured to be 50.2 ng/mL (Cmax) and 25.6 ng*day/mL (AUClast).

Table 11: Maternal Rat Serum Toxicokinetics

Dose Group	SGD-1010 Dose Level (mg/kg/dose)	N[a]	Gestational Day	C_{max} (ng/mL)	DN C_{max} (ng/mL)/(mg/kg/dose)	T_{max} (Day)	$AUC_{0\text{-last}}$ (ng·day/mL)	$AUC_{0\text{-1d}}$ (ng·day/mL)	DN $AUC_{0\text{-1d}}$ (ng·day/mL)/(mg/kg/dose)
12	0.2	9	6	29.7	148	0.00347	16.2	16.2	80.9
			13	50.2	251	0.00347	25.6	25.6	128

a Total number of animals. Blood from 3 animals/timepoint was collected.

(Applicant Table reproduced from Study 8204397)

Placental Transfer Following Two Weekly Doses of SGD-1010

SGD-1010 concentrations in amniotic fluid and fetal serum on GD 18 were higher than those in maternal rat serum, indicating that SGD-1010 is transferred from maternal rat serum to fetus.

Table 12: Ratio of SGD-1010 Concentration in Amniotic Fluid and Fetal Serum to Maternal Serum on GD 18

Dose Group	SGD-1010 Dose Level (mg/kg/dose)	Animal Number	Ratio Amniotic Fluid:Maternal Serum	Ratio Fetal Serum:Maternal Serum
12	0.2	B57515	NA	NA
		B57516	NA	0.0137:BLQ
		B57517	NA	0.0180:BLQ
		B57518	0.0151:BLQ	0.0141:BLQ
		B57519	0.0205:BLQ	NA
		B57520	NA	NA
		B57521	0.0192:BLQ	0.0132:BLQ
		B57522	NA	NA
		B57523	NA	NA

NA Not applicable, it was not possible to calculate ratios when the observed concentrations were below the lower limit of quantitation (BLQ).

(Applicant Table reproduced from Study 8204397)

9.3 Prenatal and Postnatal Development

None

10 Special Toxicology Studies

Study title/No: Tissue Cross-Reactivity of DCDS4501A with Human Tissues Ex Vivo/10-0711

In this study, polatuzumab vedotin at 2.5 and 12.5 µg/mL was applied on cryosections of full panels of human tissues from 3 separate individuals and binding was determined immunohistochemically using a biotinylated mouse anti-MMAE secondary antibody. Polatuzumab vedotin tissue distribution is consistent with the reported expression

pattern of CD79b showing specific reactivity particularly those in B-cell areas, lymph nodes, spleen, tonsil, and the GALT in the stomach, colon, and gastrointestinal tract.

Study title/No: SGD-1006, SGD-1427 and SGD-1010 photosafety evaluation/TRN-2926-A

The photosafety of SGD-1006 (vc-MMAE), SGD-1427 (NAC-vcMMAE), and a subsequent study to evaluate SGD-1010 (MMAE) was assessed. MMAE and vcMMAE did not absorb light within the range of natural sunlight (290-700 nm).

11 Integrated Summary and Safety Evaluation

See Executive Summary.

12 Appendix/Attachments

None.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

RAMADEVI GUDI
05/21/2019 08:34:28 AM

NATALIE E SIMPSON
05/21/2019 08:38:47 AM

CHRISTOPHER M SHETH
05/21/2019 08:39:55 AM
I concur