CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761035Orig1s000

PHARMACOLOGY REVIEW(S)

MEMORANDUM

Empliciti (elotuzumab)

Date: November 4, 2015
To: File for BLA 761035
From: John K. Leighton, PhD, DABT
Director, Division of Hematology Oncology Toxicology
Office of Hematology and Oncology Products

I have examined pharmacology/toxicology supporting and labeling reviews for Empliciti conducted by Dr. Manning, and secondary memorandum and labeling provided by Dr. Sheth. I concur with Dr. Sheth conclusion that Empliciti may be approved for the proposed indication.

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/s/

JOHN K LEIGHTON
11/04/2015

MEMORANDUM

Date: October 26, 2015
From: Christopher Sheth, PhD
Division of Hematology Oncology Toxicology (DHOT)
Office of Hematology and Oncology Products (OHOP)
Re: Approvability for Pharmacology and Toxicology
NDA: 761035
Drug: Empliciti (elotuzumab) for injection, for intravenous use
Indication: Empliciti is indicated in combination with lenalidomide and dexamethasone for the treatment of multiple myeloma in patients who have received one to three prior therapies
Applicant: Bristol-Myers Squibb Company

Elotuzumab is a humanized IgG1 monoclonal antibody directed against the cell surface glycoprotein Signaling Lymphocyte Activation Molecule F7 (SLAMF7) being developed for the treatment of multiple myeloma. Empliciti will be supplied as lyophilized powder for reconstitution in 300 and 400 mg single use vials. Empliciti will be administered with lenalidomide and dexamethasone at 10 mg/kg intravenously every week for the first two cycles and every 2 weeks thereafter, until disease progression or unacceptable toxicity. Patients taking Empliciti will be premedicated with dexamethasone, diphenhydramine, ranitidine and acetaminophen.

SLAMF7 is primarily expressed on natural killer cells, and on normal and malignant plasma cells (including myeloma cells). The results of pharmacology studies reviewed suggest elotuzumab exerts anti-myeloma activity through two characterized mechanisms of action, both involving natural killer cells. One mechanism involves direct activation (in a process that includes binding of elotuzumab to SLAMF7 on natural killer cells and involves the Fc region of the antibody). The other mechanism involves elotuzumab binding to SLAMF7 on myeloma cells, and eliciting antibody-dependent cellular cytotoxicity when in the presence of natural killer cells. The combination of elotuzumab and lenalidomide appeared to elicit enhanced activation of natural killer cells in vitro. In vivo antitumor activity was studied in mouse xenograft models, showing the activity of elotuzumab and lenalidomide was greater than the effects of either agent alone.

Human and nonhuman tissue cross-reactivity assessments indicated that elotuzumab does not cross-react with any of the nonhuman tissues tested, which included the common laboratory animal species. A single dose monkey toxicology study examined the potential for off-target effects of infused elotuzumab, and elotuzumab was well tolerated. Nothing adverse was noted in the local tolerance and hemolysis evaluations. Cytokine release was noted in human blood exposed to elotuzumab. The risk of infusion reactions is clearly stated on the label for Empliciti and premedication prophylaxis is recommended (see full prescribing information).

The Applicant's proposal for Section 8 of the label is consistent with the Pregnancy and Lactation Labeling Rule. The label for Empliciti contains a Warning and Precaution for

combination use, and recommends reading the full prescribing information for lenalidomide, as inclusion of lenalidomide in the regimen poses a risk of embryo-fetal harm.

No genotoxicity studies were conducted with elotuzumab (as per ICH S6) and no carcinogenicity were conducted with elotuzumab (as per ICH S6 and S9). The label for Empliciti contains a Warning and Precaution for second primary malignancies observed in patients. Due to the lack of pharmacologically relevant species, and because animal studies of fertility, early embryonic development and pre- and post-natal effect are not generally warranted to support marketing of pharmaceuticals intended for the treatment of patients with advanced cancer (as per ICH S9), these types of studies were not conducted with elotuzumab.

The nonclinical studies needed to support product labeling were reviewed by Dr. Michael Manning. The nonclinical findings are summarized in the "Executive Summary" of the BLA review and reflected in the product label. The Established Pharmacological Class of "SLAMF7-directed immunostimulatory antibody" was determined to be both scientifically valid and clinically meaningful for elotuzumab.

Recommendation: I concur with the pharmacology/toxicology reviewer that from a nonclinical perspective, Empliciti may be approved and that no additional nonclinical studies are needed to support approval of Empliciti in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received one to three prior therapies.

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/s/

CHRISTOPHER M SHETH
11/02/2015

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:	761035
Supporting document/s:	2
Applicant's letter date:	June 29, 2015
CDER stamp date:	June 29, 2015
Product:	Empliciti (elotuzumab)
Indication:	Empliciti is indicated in combination with lenalidomide and dexamethasone for the treatment of multiple myeloma in patients who have received one to three prior therapies
Applicant:	Bristol-Myers Squibb Company
Review Division:	Division of Hematology Oncology Toxicology (DHOT) for Division of Hematology Products (DHP)
Reviewer:	Michael L Manning, PhD
Supervisor/Team Leader:	Christopher M Sheth, PhD
Division Director:	John Leighton, PhD, DABT Ann Farrell, MD (DHP)
Project Manager:	Natasha Kormanik, MSN, RN, OCN

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of BLA 761035 are owned by Bristol-Myers Squibb Company or are data for which Bristol-Myers Squibb Company has obtained a written right of reference. Any information or data necessary for approval of BLA 761035 that Bristol-Myers Squibb Company does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of BLA 761035.

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1 Executive Summary

1.1 Introduction

This application is a 351(a) BLA for elotuzumab (Empliciti). Elotuzumab is a first-in-class monoclonal antibody directed against the cell surface glycoprotein Signaling Lymphocyte Activation Molecule F7 (SLAMF7) which is primarily expressed on Natural Killer (NK) and normal and malignant plasma cells. The Applicant proposes elotuzumab be indicated for adult patients with multiple myeloma who have received one to three prior therapies, and be administered in combination with lenalidomide and dexamethasone. Elotuzumab has not been marketed or withdrawn in any other country.

1.2 Brief Discussion of Nonclinical Findings

Elotuzumab binds SLAMF7 expressed on human plasma cells, NK cells, NKT cells, $CD8^+$ T cells, and $CD4^+$ T cells, but does not bind to any other human tissue element or cross-react with SLAMF7 from any non-human species tested. Binding of elotuzumab to SLAMF7 on NK cells in vitro caused upregulation of CD69, increased cytokine production, and degranulation, implicating direct NK cell activation as a mechanism of action. Elotuzumab also binds SLAMF7-expressing multiple myeloma cell lines in vitro, and in the presence of NK cells, mediates antibody-dependent cellular cytotoxicity (ADCC). Elotuzumab does not bind or kill cells deficient in SLAMF7. Complement-dependent cytotoxicity (CDC) does not contribute to elotuzumab-mediated cell killing, but other mechanisms of action cannot be definitively excluded.

The in vivo anti-tumor activity of elotuzumab and the parental murine antibody MuLuc63 was studied in xenograft mouse models with tumors grown from the human multiple myeloma cell lines L363 and OPM2. Both elotuzumab and MuLuc63 exhibited anti-tumor activity, however MuLuc63 was more potent. The Applicant attributed the difference in activity to increased ADCC mediated by MuLuc63 as murine NK cells interact more efficiently with the Fc region of MuLuc63 than elotuzumab. In the OPM2 xenograft mouse model elotuzumab mediated maximal anti-tumor activity at the 10 mg/kg dose level, the highest dose level tested. The 10 mg/kg dose level correlated with minimal and maximal elotuzumab serum concentrations of 70 µg/mL and 430 µg/mL, respectively. In subsequent clinical studies investigators sought a trough serum elotuzumab concentration of ≥70 µg/mL, which was achieved in patients at the proposed 10 mg/kg dose level. The anti-tumor activity of elotuzumab was also studied in combination with bortezomib and in combination with lenalidomide. Elotuzumab, bortezomib, and lenalidomide each conferred similar anti-tumor activity in the OPM2 xenograft mouse model, however when elotuzumab was combined with either bortezomib or lenalidomide enhanced anti-tumor activity was observed. These nonclinical findings support the combination of elotuzumab with (b) (4) lenalidomide. (b) (4)

(b) (4)

(b) (4)

Due to the lack of a pharmacologically-relevant animal species to conduct toxicology studies, the scope of the toxicological evaluation for elotuzumab was limited to a tissue cross-reactivity study and in vivo studies that assessed the potential for off-target toxicity and local tolerance. In the human tissues examined, elotuzumab stained the membrane and/or cytoplasm of plasma cells and/or immunoblasts in the bone marrow, breast, cervix, esophagus, Fallopian tube, gastrointestinal tract, liver, lymph node, pancreas, salivary gland, small intestine, spleen, stomach, thymus, thyroid, tonsil, ureter, and uterus. A single dose of intravenously infused elotuzumab (0, 30, or 100 mg/kg) was well tolerated in rhesus monkeys with no clinical signs at any dose. There were no local adverse reactions when 5 mg of elotuzumab was intravenously injected into the ears of New Zealand white rabbits, and a solution of 10 mg/mL elotuzumab did not cause hemolysis of human whole blood. An in vitro cytokine release experiment identified elevated levels of 10 cytokines in response to elotuzumab treatment. The results of the aforementioned toxicology studies indicate elotuzumab presents little risk of off-target toxicity or a significant local adverse reaction when administered by intravenous injection.

With prior agreement with the FDA, the Applicant did not conduct carcinogenicity, genotoxicity, safety pharmacology, repeat dose toxicity, or reproductive and developmental toxicity studies with elotuzumab. Carcinogenicity studies are not necessary to support the marketing of therapeutics intended to treat patients with advanced cancer as discussed in the ICH S9 guidance document. Genotoxicity studies are generally not necessary to support marketing of biotechnology-derived pharmaceuticals such as elotuzumab as discussed in the ICH S6 guidance document. Safety pharmacology, repeat dose toxicity, and reproductive and developmental toxicity studies were not conducted due to the lack of a pharmacologically-relevant animal species.

The Applicant submitted a risk assessment for the potential for reproductive and developmental toxicity for elotuzumab based on the tissue distribution of SLAMF7 and published literature. SLAMF7 is expressed on plasma cells and immunoblasts in the uterus and cervix, however the implications for reproduction in vivo are unknown. Elotuzumab is an IgG1 monoclonal antibody, which as a class have the potential to cross the placental barrier permitting direct fetal exposure. The impact of elotuzumab on fetal development is unknown, however published reports indicate SLAMF7-deficient mice appear healthy suggesting SLAMF7 does not play a role in embryo-fetal development.

1.3 Recommendations

1.3.1 Approvability

The nonclinical studies submitted to this BLA provide sufficient information to support the use of Empliciti, in combination with lenalidomide and dexamethasone, for the

treatment of adult patients with [redacted] multiple myeloma. From the nonclinical pharmacology and toxicology perspective, Empliciti is recommended for approval.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

The content for the labeling of Empliciti is supported by the studies submitted to BLA 761035 and is contained in this review. The Applicant's proposed Established Pharmacologic Class (EPC) of "SLAMF7-directed immunostimulatory antibody" was determined to be both clinically meaningful and scientifically valid for Empliciti.

2 Drug Information

2.1 Drug

CAS Registry Number: 915296-00-3

Generic Name: Elotuzumab

Code Name: BMS-901608, 4115, 4117, DS001, HuLuc63, anti-CS1

Chemical Name: Anti-SLAMF7 humanized monoclonal antibody

Molecular Formula: [redacted]

Molecular Weight: 148090 Daltons [redacted]

Structure or Biochemical Description:

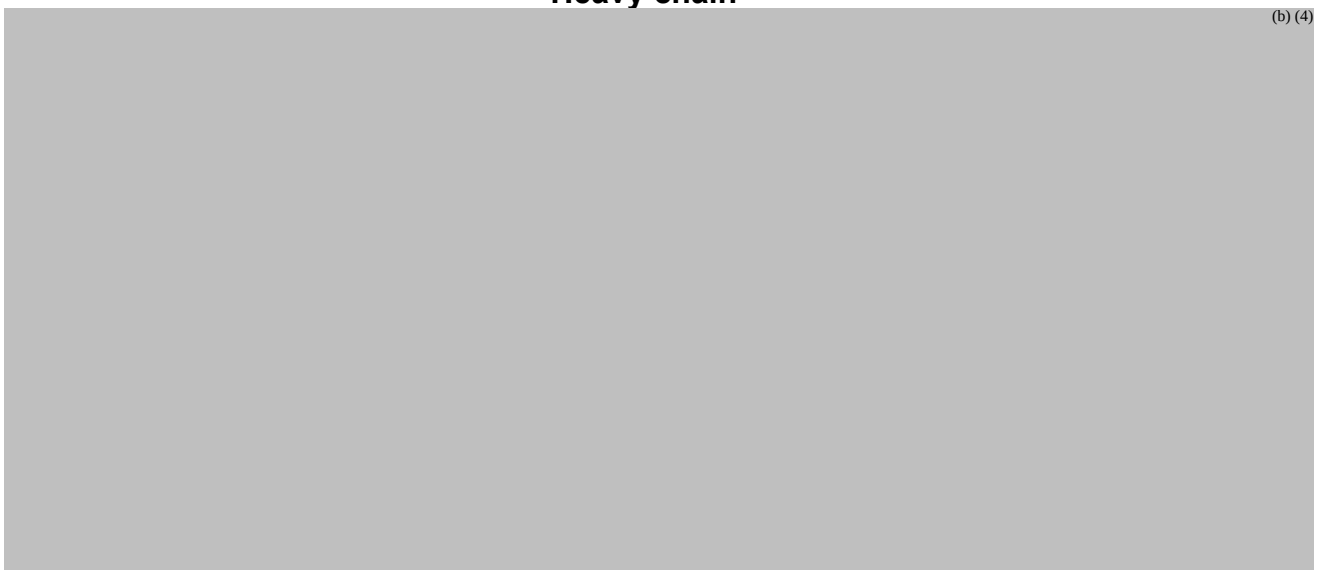
Elotuzumab is a humanized IgG1 monoclonal antibody directed against the cell surface glycoprotein SLAMF7 of human origin. The elotuzumab molecule consists o [redacted]. The antibody was constructed by grafting the complementarity-determining regions (CDRs) from the parental murine antibody MuLuc63 onto the human IgG1 heavy and kappa light chain framework regions. Based on the amino acid sequence provided by the Applicant (see Figure 2), elotuzumab has an isoelectric point of [redacted] and a theoretical extinction coefficient of [redacted] mL mg^{-1} cm^{-1}.

Pharmacologic Class: SLAMF7-directed immunostimulatory antibody

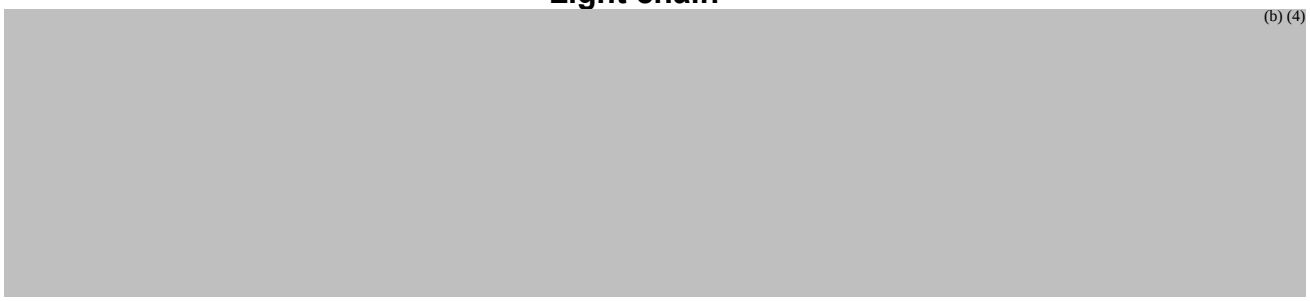
Figure 1: Domain structure of elotuzumab

Figure 2: Primary amino acid sequence of elotuzumab

Heavy chain



Light chain



2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 100043

2.3 Drug Formulation

The elotuzumab drug substance is a sterile, non-pyrogenic, lyophilized powder provided in vials containing 300 mg or 400 mg elotuzumab. The elotuzumab drug p (b) (4) packaged in a single-use 20 cc Type I glass vial, stoppered with a 20 mm rubber stopper, and sealed with a 20 mm aluminum crimp seal. The lyoph elotuzumab drug substance is reconstituted with sterile water for injection to obtain a solution with a protein concentration of 25 mg/mL. Prior to intravenous administration, the reconstituted elotuzumab solution is aseptically diluted with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP (b) (4) The composition of the elotuzumab drug product, including the quality standard, function, and quantity of each component is listed in Table 1.

Table 1: Composition of the elotuzumab drug product

Component	Quality standard	Function	Quantity per vial[a]	
			400 mg	300 mg
Elotuzumab	BMS Specification	Active ingredient	(b) (4)	
Sodium citrate[b]	USP, Ph.Eur., JP	(b) (4)	21.5 mg	16.6 mg
Citric acid monohydrate	USP, Ph.Eur., JP		3.17 mg	2.44 mg
Sucrose	NF, Ph.Eur., JP		660 mg	510 mg
Polysorbate 80	NF, Ph.Eur., JP		4.40 mg	3.40 mg
Water for injection[c]	USP, Ph.Eur.		(b) (4)	
(b) (4)	NF, Ph.Eur.			

[a] Each vial contains a (b) (4) mL overfill for vial, needle, and syringe holdup.
[b] Sodium citrate dihydrate is used
(b) (4)

Abbreviations: USP = United States Pharmacopoeia; Ph.Eur. = European Pharmacopoeia NF = National Formulary; JP = Japanese Pharmacopoeia; (b) (4)

2.4 Comments on Novel Excipients

None

2.5 Comments on Impurities/Degradants of Concern

None

2.6 Proposed Clinical Population and Dosing Regimen

The proposed clinical population is adult patients with multiple myeloma who have received one to three prior therapies. Empliciti is to be administered in combination with lenalidomide and dexamethasone. When administered with lenalidomide and dexamethasone, the dose of Empliciti is 10 mg/kg administered intravenously every week for the first two cycles and every 2 weeks thereafter until disease progression or unacceptable toxicity. Patients should be premedicated with dexamethasone, diphenhydramine, ranitidine and acetaminophen prior to infusion with Empliciti.

2.7 Regulatory Background

Meetings with the FDA include an End of Phase 2 meeting on February 15, 2011 and a pre-Phase 3 meeting on October 17, 2012. A pre-BLA meeting was held on March 9, 2015.

Elotuzumab was granted Orphan Drug Designation for the treatment of patients with multiple myeloma on September 1, 2011 and Breakthrough Therapy Designation on May 12, 2014. The proposed proprietary name, Empliciti, was conditionally approved on September 16, 2015.

On May 20, 2015 Rolling Review was granted for BLA 761035. The first two modules were submitted on May 27, 2015 and the final three modules were submitted on June 29, 2015.

3 Studies Submitted

3.1 Studies Reviewed

Pharmacology

Study number	Study title	eCTD location
RTR5	BIAcore-Based Affinity Measurements of the Parental Murine Anti-Human CS1 Antibody, MuLuc63, and Its Humanized Version, HuLuc63, to Purified Recombinant Human CS1 Protein	4.2.1.1.
RTR8	HuLuc63 Binding to Immune Subsets in Human Whole Blood	4.2.1.1.
RTR9	HuLuc63 Binding to Immune Subsets in Whole Blood and Bone Marrow Samples from Multiple Myeloma Patients	4.2.1.1.
RTR12	HuLuc63 Cross-Reactivity in Human and Non-Human Tissues Using Immunohistochemistry (IHC)	4.2.1.1.
RTR18	HuLuc63 Cross-Reactivity Study on Recombinant CS1 from Non-Human Primates	4.2.1.1.
RTR13	Analysis of ADCC and CDC Activity of HuLuc63	4.2.1.1.
Collins et al.	Elotuzumab directly enhances NK cell cytotoxicity against myeloma via CS1 ligation: evidence for augmented NK cell function complementing ADCC	N/A
RTR14	In Vivo Anti-Tumor Efficacy of MuLuc63 and Its Humanized Version, HuLuc63	4.2.1.1.

Study number	Study title	eCTD location
RTR26	Increased Anti-Tumor Activity of HuLuc63 in Combination with Bortezomib in the OPM-2 Xenograft Model	4.2.1.1.
Balasa et al.	Elotuzumab enhances natural killer cell activation and myeloma cell killing through interleukin-2 and TNF-α pathways	N/A

Pharmacokinetics

Study number	Study title	eCTD location
RTR15	Determination of Minimal and Optimal Serum Levels of HuLuc63 Required for In Vivo Anti-Tumor Efficacy in a Mouse Xenograft Model	4.2.2.7.

Toxicology

Study number	Study title	eCTD location
TR07150	Sing e Dose Intravenous Infusion Toxicity and Toxicokinetics Study with HuLuc63 in Rhesus Monkeys	4.2.3.1.
TR06051	Final Immunopathology Report Cross-Reactivity of HuLuc63 with Normal Human Tissues	4.2.3.7.7.
TR06050	Local Tolerance Study in Rabbits (Intravenous Injection) with HuLuc63	4.2.3.6.
R&D/14/ 0759	n vitro cytokine analysis of elotuzumab-treated primary immune cells	5.3.1.4.
TR06047	Hemolysis Assay in Human Whole Blood with HuLuc63	4.2.3.7.7.

3.2 Studies Not Reviewed

Pharmacology

Study number	Study title	eCTD location
DP-5348	n vivo studies on the combination of elotuzumab with lirilumab	4.2.1.1.
IO00047	ncreased anti-tumor activity of elotuzumab in combination with pomalidomide or dexamethasone in the OPM2 xenograft model	4.2.1.1.
OPM-2	Non-Clinical Evaluation of the Combination of Elotuzumab with CD 137 Agonist Monoclonal Antibody in a Model of Multiple Myeloma	4.2.1.1.
RTR10	MuLuc63 Staining of Normal Human Tissues Using Immunohistochemistry	4.2.1.1.
RTR11	MuLuc63 Staining of Plasmacytomas Using Immunohistochemistry	4.2.1.1.
RTR16	HuLuc63-Mediated Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC) Against L-363 Cells Using PBMCs from Multiple Myeloma Patients as Effectors	4.2.1.1.
RTR21	HuLuc63 Binding to Immune Subsets in Whole Blood Samples of Non-Human Primates	4.2.1.1.
RTR3	Generation of Humanized Anti-CS1 Monoclonal Antibody HuLuc63 IgG1/k	4.2.1.1.

Pharmacokinetics

Study number	Study title	eCTD location
TR06012	Validation of an ELISA to Quantitate HuLuc63 in Mouse Serum	4.2.1.1.

Study number	Study title	eCTD location
TR06044	Qualification of an ELISA to Quantitate HuLuc63 in Rhesus Serum	4.2.1.1.
TR08248	Partial Validation of an ELISA for the Quantitation of HuLuc63 in Mouse Serum following Relocation of PDL BioPharma	4.2.1.1.
TR06011	Determination of HuLuc63 SCID Mouse Serum Concentrations in Support of Study CS1.T.MH.057	4.2.2.7.

Toxicology

Study number	Study title	eCTD location
RTR19	Effects of HuLuc63 In Vitro on Lymphocyte Subsets in Whole Blood from Healthy Human Donors	4.2.3.7.2.
RTR20	Evaluation of the Effect of HuLuc63 on Erythroid and Myeloid Progenitors from Anal sed Bone Marrow of Three Normal Donors Using Methylcellulose-Based n Vitro Colony Assays	4.2.3.7.2.
RD-14-0940	Generation of hCS1 Transgenic Mice	4.2.3.7.7.
TR06052	Final Preliminary Studies Report Method Qualification Study to Establish the Conditions for Cross-Reactivity of HuLuc63 with Normal Human, Chimpanzee, and Rhesus Monkey Tissues	4.2.3.7.7.

3.3 Previous Reviews Referenced

None

4 Pharmacology

4.1 Primary Pharmacology

Study title: BIAcore-Based Affinity Measurements of the Parental Murine Anti-Human CS1 Antibody, MuLuc63, and its Humanized Version, HuLuc63, to Purified Recombinant Human CS1 Protein

Study no.:	RTR5
Report date:	May 18, 2006
Study report location:	eCTD 4.2.1.1.
Conducting laboratory:	PDL BioPharma Inc. 34801 Campus Dr. Fremont, CA 94555
GLP compliance:	No

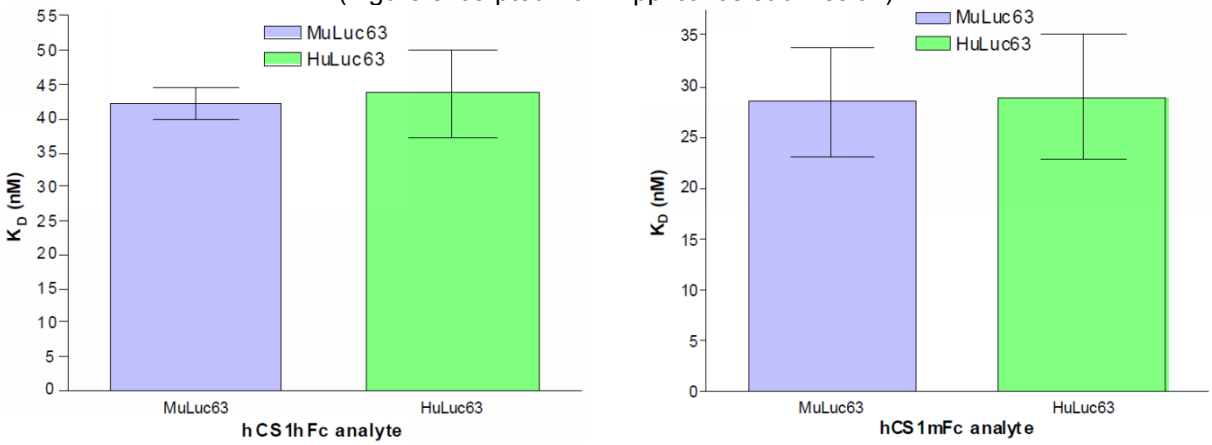
The objective of the study was to define and compare the binding affinities of HuLuc63 and the parental murine monoclonal antibody MuLuc63 to purified recombinant human CS1-Fc protein. Recombinant human CS1 was fused to both human and murine Fc regions. Binding affinities were determined by surface plasmon resonance.

Results and Conclusions

- MuLuc63 and HuLuc63 similarly bind purified recombinant human CS1 fused to a human Fc region with a K_D ~45 nM (see Figure 3).
- MuLuc63 and HuLuc63 similarly bind purified recombinant human CS1 fused to a murine Fc region with a K_D ~30 nM.
- MuLuc63 and HuLuc63 similarly bind CS1-Fc irrespective of species origin of Fc region, implying MuLuc63 and HuLuc63 bind CS1 rather than the Fc region.

Figure 3: The binding affinity of MuLuc63 and HuLuc63 to human CS1 fused to human and murine Fc regions

(Figure excerpted from Applicant's submission)



Left: CS1-Fc (human Fc region); Right: CS1-Fc (murine Fc region)

Study title: HuLuc63 Binding to Immune Subsets in Human Whole Blood

Study no.:	RTR8
Report date:	May 26, 2006
Study report location:	eCTD 4.2.1.1.
Conducting laboratory:	PDL BioPharma Inc. 34801 Campus Dr. Fremont, CA 94555
GLP compliance:	No

The objective of the study was to examine the binding of FITC-labeled HuLuc63 to various leukocytes in whole blood samples from healthy adult humans using flow cytometry.

Table 2: Markers used to define leukocyte subsets in whole blood samples from healthy adult humans

Leukocyte subset	Markers
NK cells	$CD3^-CD16^+CD56^+$
NKT cells	$CD3^+CD16^+CD56^+$
CD8+T cells	$CD3^+CD8^+$
CD4+ T cells	$CD3^+CD8^-$ or $CD3^+CD4^+$
Monocytes	$CD14^+$HLA-DR^+
B cells	$CD20^+$HLA-DR^+
Granulocytes	$CD3^-CD45^+CD13^+$

Results and Conclusions

- FITC-labeled HuLuc63 bound to the majority of NK, NKT, and $CD8^+$ T cells in whole blood samples from healthy adult humans (see Table 3).
- FITC-labeled HuLuc63 bound to a lower percentage of $CD4^+$ T cells, and did not bind B cells, monocytes or granulocytes to any appreciable degree.

Table 3: HuLuc63-FITC binding to leukocytes in whole blood samples from healthy adult humans

Leukocyte subset	%HuLuc63 binding Mean ± SD (n)
NK cells	93.6 ± 3.1 (9)
NKT cells	90.0 ± 12.5 (9)
$CD8^+$ T cells	53.5 ± 18.4 (9)

Leukocyte subset	%HuLuc63 binding Mean ± SD (n)
$CD4^+$ T cells	11.5 ± 6.1 (9)
Monocytes	6.6 ± 4.2 (11)
B cells	3.0 ± 1.4 (11)
Granulocytes	0.15 ± 0.1 (4)

Study title: HuLuc63 Binding to Immune Subsets in Whole Blood and Bone Marrow Samples from Multiple Myeloma Patients

Study no.: RTR9
Report date: June 6, 2006
Study report location: eCTD 4.2.1.1
Conducting laboratories: (b) (4)
GLP compliance: No

The objective of the study was to examine the binding of FITC-labeled HuLuc63 to various leukocytes in whole blood and bone marrow samples from patients with multiple myeloma using flow cytometry.

Table 4: Markers used to define leukocyte subsets in whole blood and bone marrow samples from patients with multiple myeloma

Leukocyte subset	Markers
NK cells	$CD3^-CD16^+CD56^+$
NKT cells	$CD3^+CD16^+CD56^+$
CD8+T cells	$CD3^+CD8^+$
CD4+ T cells	$CD3^+CD8^-$ or $CD3^+CD4^+$
B cells	$CD20^+$HLA-DR^+
Monocytes	$CD14^+$HLA-DR^+
Stem cells	$CD45^+CD34^+$
Plasma cells	$CD138^+CD45^{-/dim\ to\ +}$

Results and Conclusions

- FITC-labeled HuLuc63 bound to the majority of NK, NKT, and $CD8^+$ T cells in bone marrow and whole blood samples from patients with multiple myeloma (see Table 5 and Table 6)
- FITC-labeled HuLuc63 bound to a lower percentage of $CD4^+$ T cells, and did not bind B cells or monocytes to any appreciable degree.
- FITC-labeled HuLuc63 bound strongly to nearly all plasma cells in bone marrow samples from patients with multiple myeloma.
- FITC-labeled HuLuc63 did not bind the hematopoietic stem cells in bone marrow samples from patients with multiple myeloma (see Table 7).
- Inter-day experimental variability may have contributed to the patient-to-patient variability.
- FITC-labeled HuLuc63 bound various leukocytes in whole blood comparably between patients with multiple myeloma and healthy adult humans (see Study no. RTR8).

Table 5: HuLuc63-FITC binding to leukocytes in bone marrow samples from patients with multiple myeloma

Donor ID	Date	$CD4^+$ T cells	$CD8^+$T cells	NKT cells	NK cells	B cells	Monocytes	Plasma cells
MM1	12/6/2005	52.8%	91.7%	93.5%	95.9%	4.5%	5.9%	*nd*
MM2	12/7/2005	23.2%	85.1%	76.6%	86.7%	5.7%	2.5%	*nd*
MM3	12/7/2005	2.5%	18.3%	50.9%	83.4%	0.7%	1.6%	*nd*
MM4	1/10/2006	34.8%	85.5%	93.9%	94.8%	5.5%	8.5%	95.6%
MM #041	11/9/2005	13.9%	93.6%	91.1%	45.5%	3.2%	0.6%	88.6%
MM #042	11/14/2005	37%	69.5%	73.5%	14.1%	3.7%	0.8%	97.1%
MM #043	11/14/2005	8.8%	78.8%	77%	13.4%	8.6%	3%	80.5%
n = 7	Mean	24.7%	74.6%	79.5%	62%	4.5%	3.3%	90.4%
	SD	17.8%	26.1%	15.3%	37%	2.4%	2.9%	7.6%

nd = not determined due to insufficient number of cells to analyze

Table 6: HuLuc63-FITC binding to leukocytes in whole blood samples from patients with multiple myeloma

Donor ID	Date	$CD4^+$ T cells	$CD8^+$T cells	NKT cells	NK cells	B cells	Monocytes	Plasma cells
MM1	1/9/2006	5.6%	70.7%	78.4%	96.6%	4.4%	2.6%	*nd*
MM2	1/11/2006	28.2%	84.6%	88.1%	93.3%	6.7%	2.5%	*nd*
MM3	1/11/2006	9.4%	61.8%	80.6%	88.6%	*nd*	6.0%	*nd*
MM4	1/13/2006	2.8%	54.8%	61.6%	93.3%	1.9%	2.9%	*nd*
MM#40	11/7/2005	0.9%	25.9%	44.2%	98.2%	1.1%	2.3%	*nd*
MM#68	5/24/2006	2.3%	42.4%	97.5%	92.8%	2.3%	1.5%	*nd*
MM#69	5/24/2006	0.9%	23.8%	77.3%	84.5%	*nd*	0.9%	*nd*
n = 7	Mean	7.1%	52.0%	75.4%	92.5%	3.3%	2.7%	---
	SD	9.8%	22.7%	17.6%	4.7%	2.3%	1.6%	---

nd = not determined due to insufficient number of cells to analyze

Table 7: HuLuc63-FITC binding to stem cells in bone marrow samples from patients with multiple myeloma

Donor ID	Stem cells	
	% $HuLuc63^+$	% Control IgG1
MM#056	0.74	0.73
MM#057	0	0
MM#058	2.3	2.35
Mean	1.01	1.03
SD	1.17	1.2

Study title: HuLuc63 Cross-Reactivity in Human and Non-Human Tissues using Immunohistochemistry (IHC)

Study no.:	RTR12
Report date:	May 19, 2006
Study report location:	eCTD 4.2.1.1.
Conducting laboratory:	PDL BioPharma Inc. 34801 Campus Dr. Fremont, CA 94555
GLP compliance:	No

A tissue cross-reactivity study was conducted to evaluate the cross-reactivity of HuLuc63 with cryosections of normal tissues of human and non-human origin (see Table 8). Results from this study provide information to select an appropriate species for HuLuc63 animal toxicology studies. HuLuc63 or human IgG1 control antibody (1.5 µg/mL) was precomplexed with biotin-SP-conjugated goat anti-human IgG (2 µg/mL), after which slides were stained with an autostainer.

Table 8: Species and tissues examined for HuLuc63 cross-reactivity

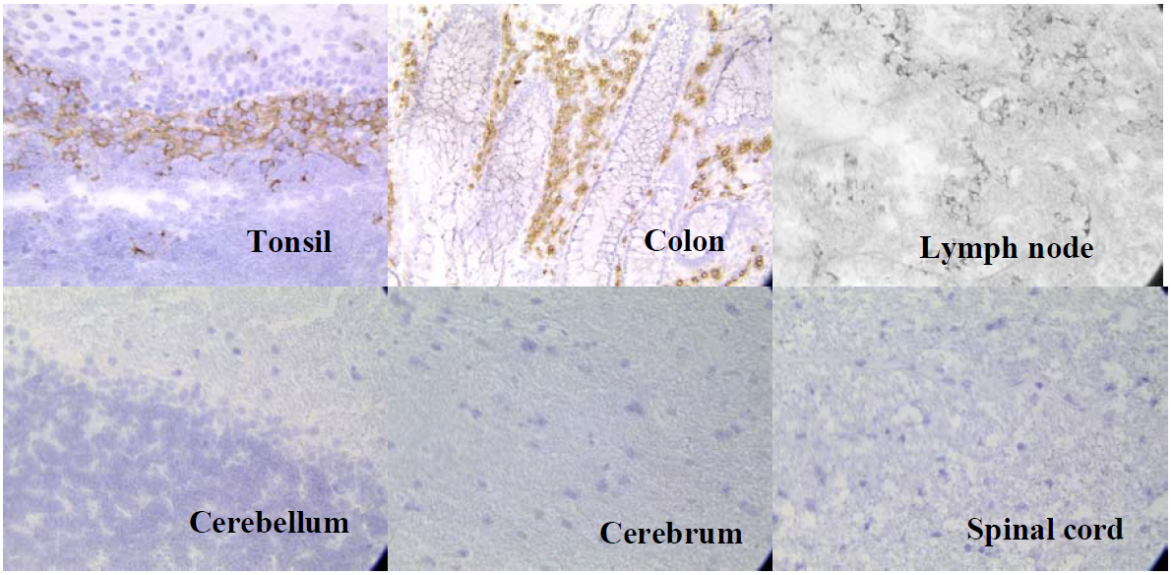
Species	Common name	Tissues
Macaca fascicularis	Cynomolgus monkey	Tonsil, spleen, and lymph node
Macaca mulatta	Rhesus monkey	Spleen, lymph node, colon, intestine and kidney
Oryctolagus cuniculus	New Zealand white rabbit	Spleen, tonsil, colon and brain
Mus musculus	CD1 mouse	Spleen, lymph node and colon
Rattus norvegicus	Sprague Dawley rat	Spleen, lymph node and colon
Canis familiaris	Beagle dog	Tonsil and spleen
Sus scrofa	Yucatan mini-pig	Tonsil, spleen and colon
Homo sapiens	Human	Tonsil, spleen, lymph node, colon, cerebrum, cerebellum, spinal cord, trigeminal ganglion and dorsal root ganglion

Results and Conclusions

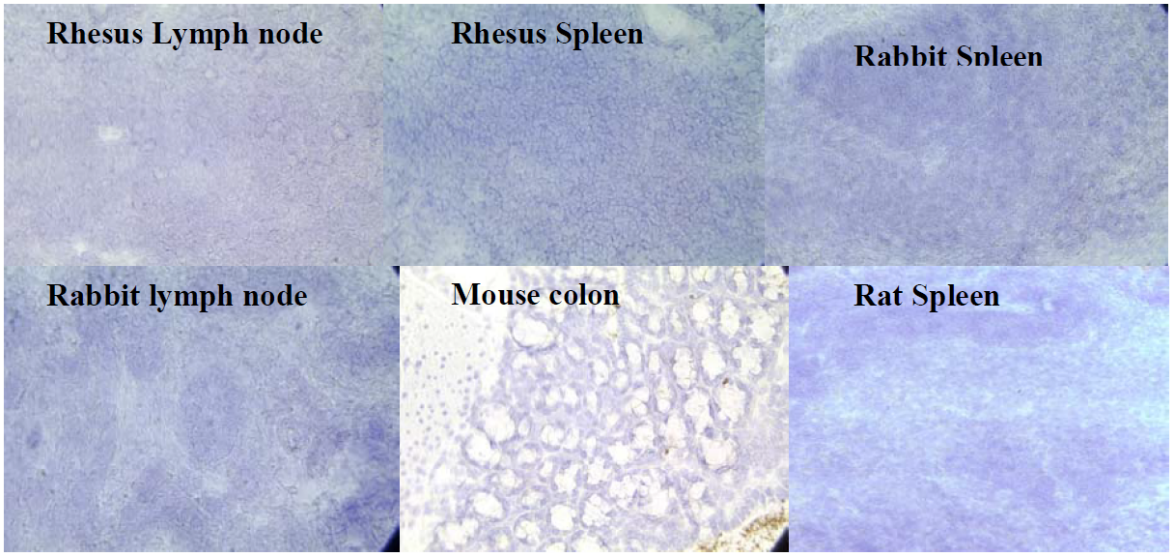
- HuLuc63-specific cell-surface staining was observed in the mononuclear cells in the following human tissues: tonsil, spleen, lymph node, colon and trigeminal ganglion (see Figure 4). The mononuclear cells which stained positive for HuLuc63 are hypothesized to be CS1-expressing plasma cells. No HuLuc63 staining was observed in the human cerebrum, cerebellum or spinal cord.
- No HuLuc63 staining was detected in any of the non-human tissues tested.
- Due to lack of cross-reactivity, none of the species examined are relevant for HuLuc63 animal toxicology studies.

Figure 4: Representative HuLuc63 staining in various human and non-human tissues

(Figure excerpted from Applicant's submission)



Human tissues



Non-human tissues

Study title: HuLuc63 Cross-Reactivity Study on Recombinant CS1 from Non-Human Primates

Study no.:	RTR18
Report date:	May 9, 2006
Study report location:	eCTD 4.2.1.1.
Conducting laboratory:	PDL BioPharma Inc. 34801 Campus Dr. Fremont, CA 94555
GLP compliance:	No

The objective of the study was to examine the cross-reactivity of HuLuc63 towards CS1 (SLAMF7) from the mouse and various non-human primates (NHP). Results from this study provide information to select an appropriate species for HuLuc63 animal toxicology studies. The binding of HuLuc63 to purified recombinant CS1 was determined by ELISA while flow cytometry was used to test the binding of HuLuc63 or MuLuc63 to full length CS1 expressed on the surface of engineered cell lines.

Table 9: Species tested for CS1 cross-reactivity

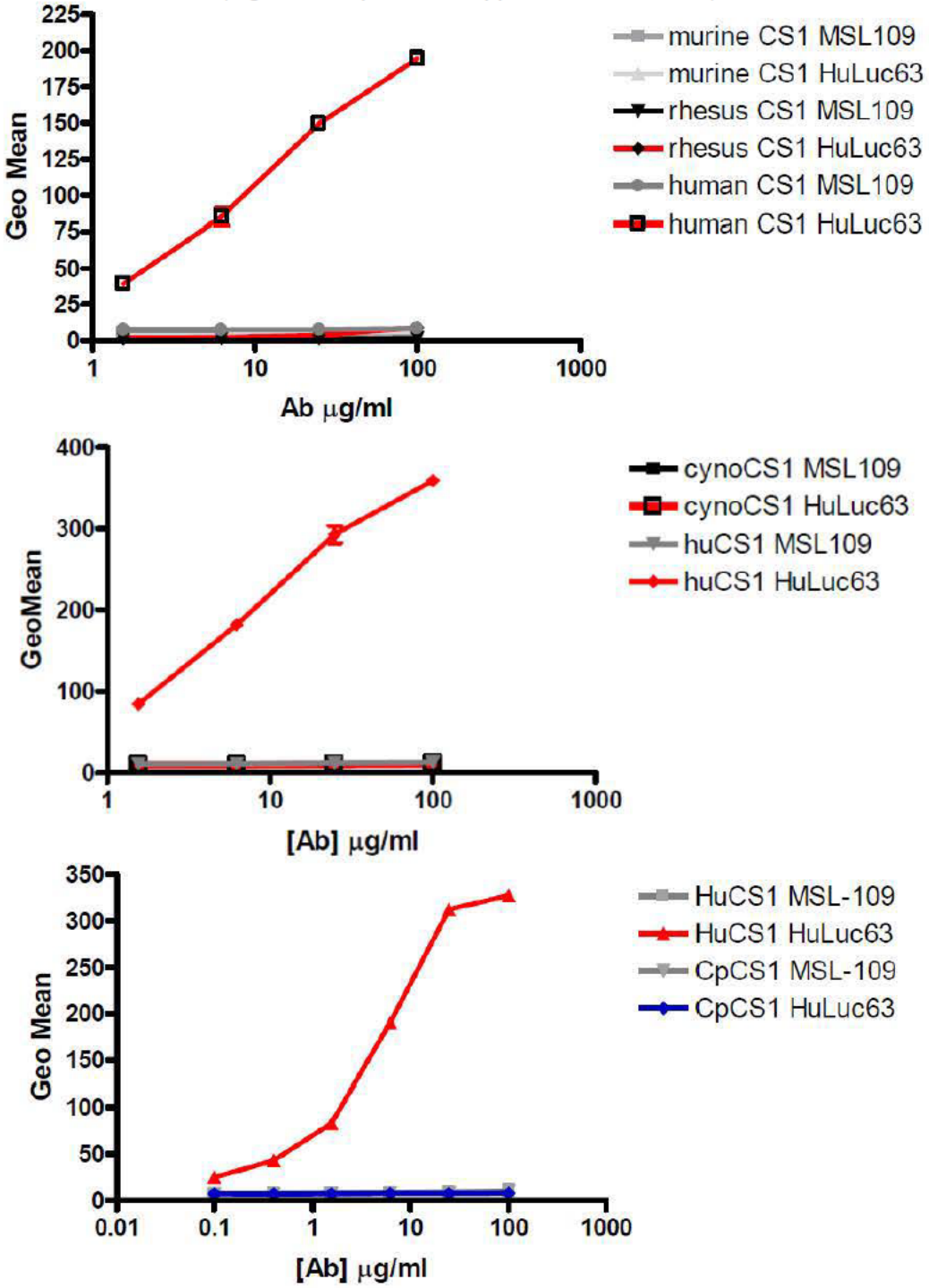
Species	CS1-Fc fusion protein (ELISA)	Cell surface expressed CS1 (flow cytometry)
Cynomolgus monkey	✓	✓
Rhesus monkey	✓	✓
Chimpanzee	✓	✓
Human	✓	✓
Mouse	✓	✓

Results and Conclusions

- HuLuc63 specifically binds only to human CS1 and does not recognize CS1 from the mouse or any NHP species tested (see Figure 5).
- The mouse, cynomolgus monkey, rhesus monkey, or chimpanzee will not serve as appropriate species for the toxicological evaluation of HuLuc63.

Figure 5: Cross-reactivity of HuLuc63 to CS1 of human, NHP, or murine origin, as assessed by flow cytometry

(Figure excerpted from Applicant's submission)



MSL109 = isotype control antibody

Top: cross-reactivity of HuLuc63 to mouse, rhesus monkey, and human CS1; middle: cross-reactivity of HuLuc63 to cynomolgus monkey and human CS1; bottom: Cross-reactivity of HuLuc63 to chimpanzee and human CS1

Study title: Analysis of ADCC and CDC Activity of HuLuc63

Study no.:	RTR13
Report date:	May 12, 2006
Study report location:	eCTD 4.2.1.1.
Conducting laboratory:	PDL BioPharma Inc. 34801 Campus Dr. Fremont, CA 94555
GLP compliance:	No

The objective of the study was to determine the mechanism of action by which HuLuc63 can mediate the specific killing of multiple myeloma cells in vitro. This study examined the potential contribution of antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and certain leukocyte subset(s) in specific cell killing.

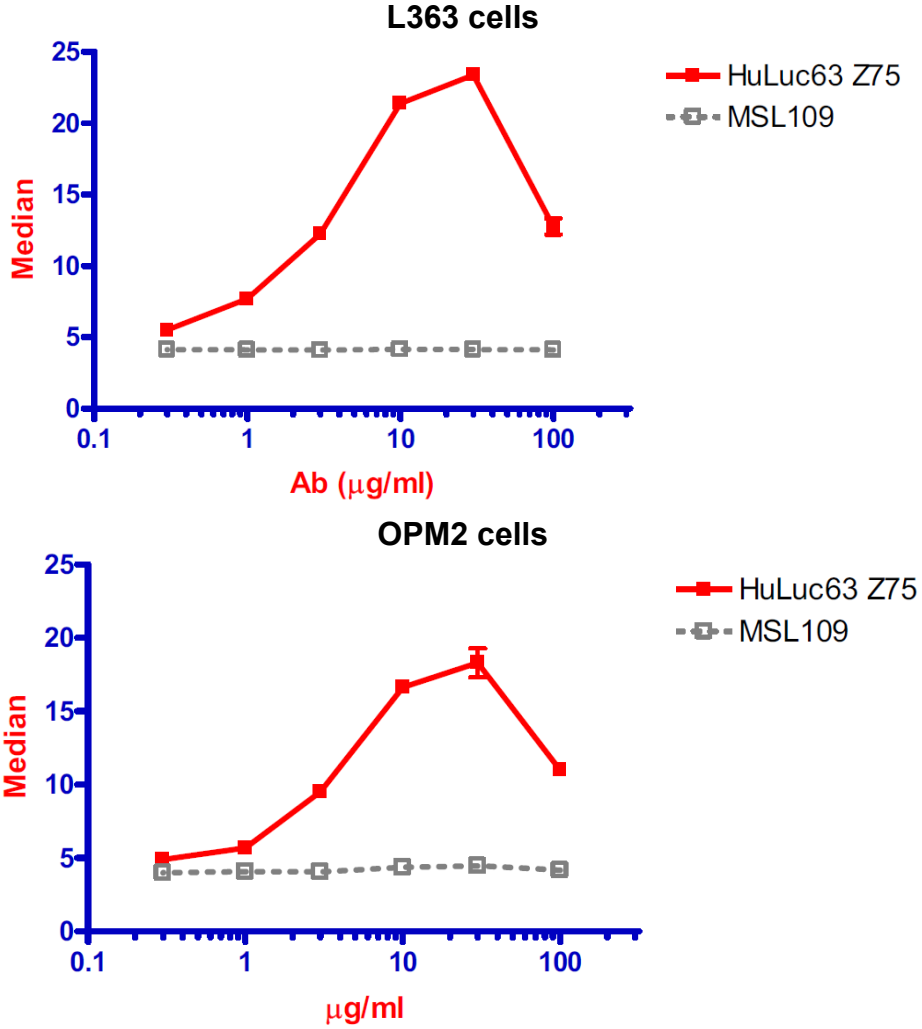
Results and Conclusions

- HuLuc63 was observed to specifically bind the SLAMF7-expressing multiple myeloma cell lines L363 and OPM2 in a concentration-dependent manner; binding of HuLuc63 reached saturation at 30 µg/mL (see Figure 6). The isotype control antibody MSL109 did not bind either multiple myeloma cell line.
- When HuLuc63 was incubated with the L363 or OPM2 multiple myeloma cell lines in the presence of human peripheral blood mononuclear cells (PBMCs), ADCC was observed, with maximal ADCC observed at 1 µg/mL (see Figure 7). The MSL109 isotype control antibody did not initiate ADCC. HuLuc63 had no apparent effect on the health or viability of the cell lines in the absence of PBMCs.
- To demonstrate the binding of HuLuc63 to cells was specific for the interaction with SLAMF7, and that this interaction mediated ADCC, cell lines deficient in SLAMF7 were transfected with cDNA encoding human SLAMF7. HuLuc63 bound cells transfected with SLAMF7 and were selectively killed by PBMCs in a HuLuc63 concentration-dependent manner (see Figure 8), while HuLuc63 did not bind the parental cell lines and were not sensitive to ADCC (data for binding was not submitted). The isotype control antibody showed no detectable binding to either the parental or transfected cell lines.
- To identify the cell subset(s) responsible for mediating ADCC, B cells, T cells, monocytes, and NK cells were individually selectively depleted from PBMCs. PBMCs depleted for NK cells showed a significant reduction in HuLuc63-mediated ADCC activity when compared to non-depleted PBMCs, while PBMCs depleted for B cells, T cells, or monocytes mediated ADCC comparable to non-depleted PBMCs (see Figure 9). The increase in antibody-independent cytotoxicity observed with PBMCs depleted in T cells is hypothesized to be the result of enriching for other leukocyte subsets.

- When HuLuc63 was added to the L363 cell line in the presence of 50% human serum, no significant CDC activity was observed compared to cells treated with an antibody with known CDC activity (see Figure 10).
- In summary, HuLuc63 can bind and kill SLAMF7-expressing cells at least in part through ADCC mediated by NK cells.

Figure 6: HuLuc63 binding to SLAMF7 on L363 and OPM2 multiple myeloma cells

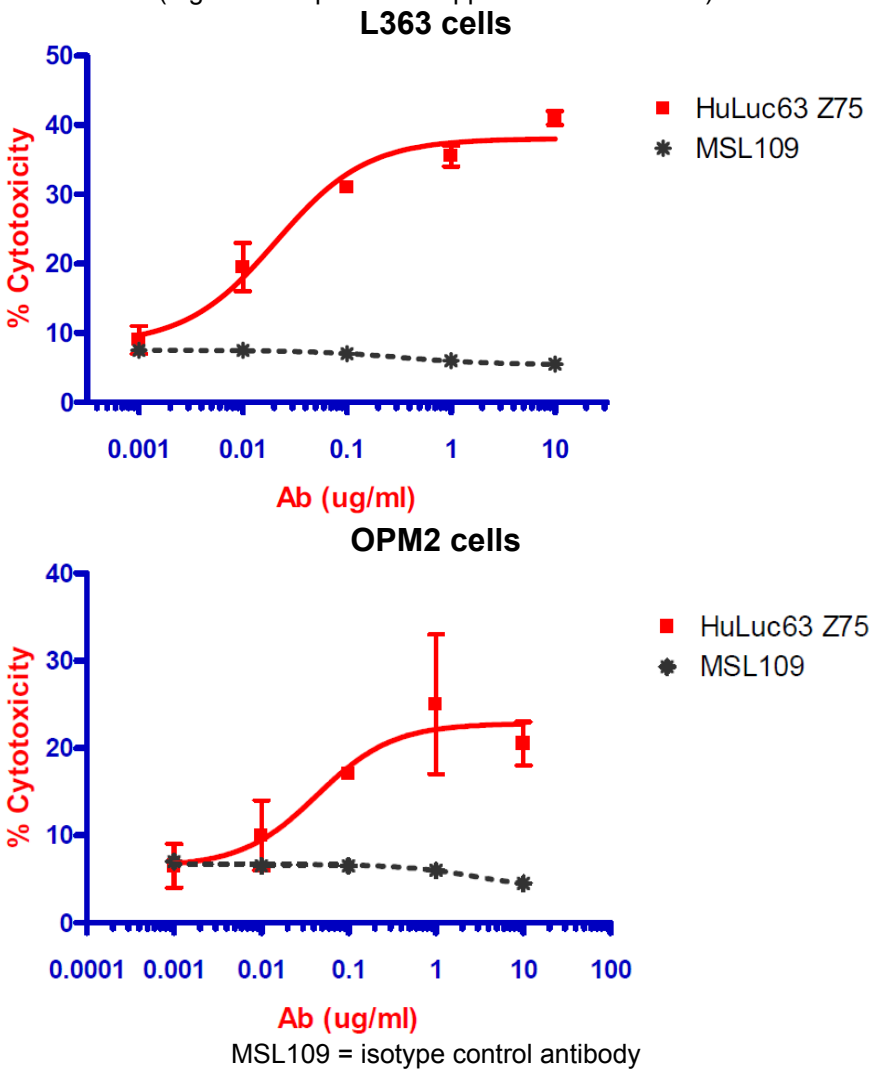
(Figure excerpted from Applicant's submission)



MSL109 = isotype control antibody

Figure 7: HuLuc63-mediated ADCC against multiple myeloma target cells by human PBMCs

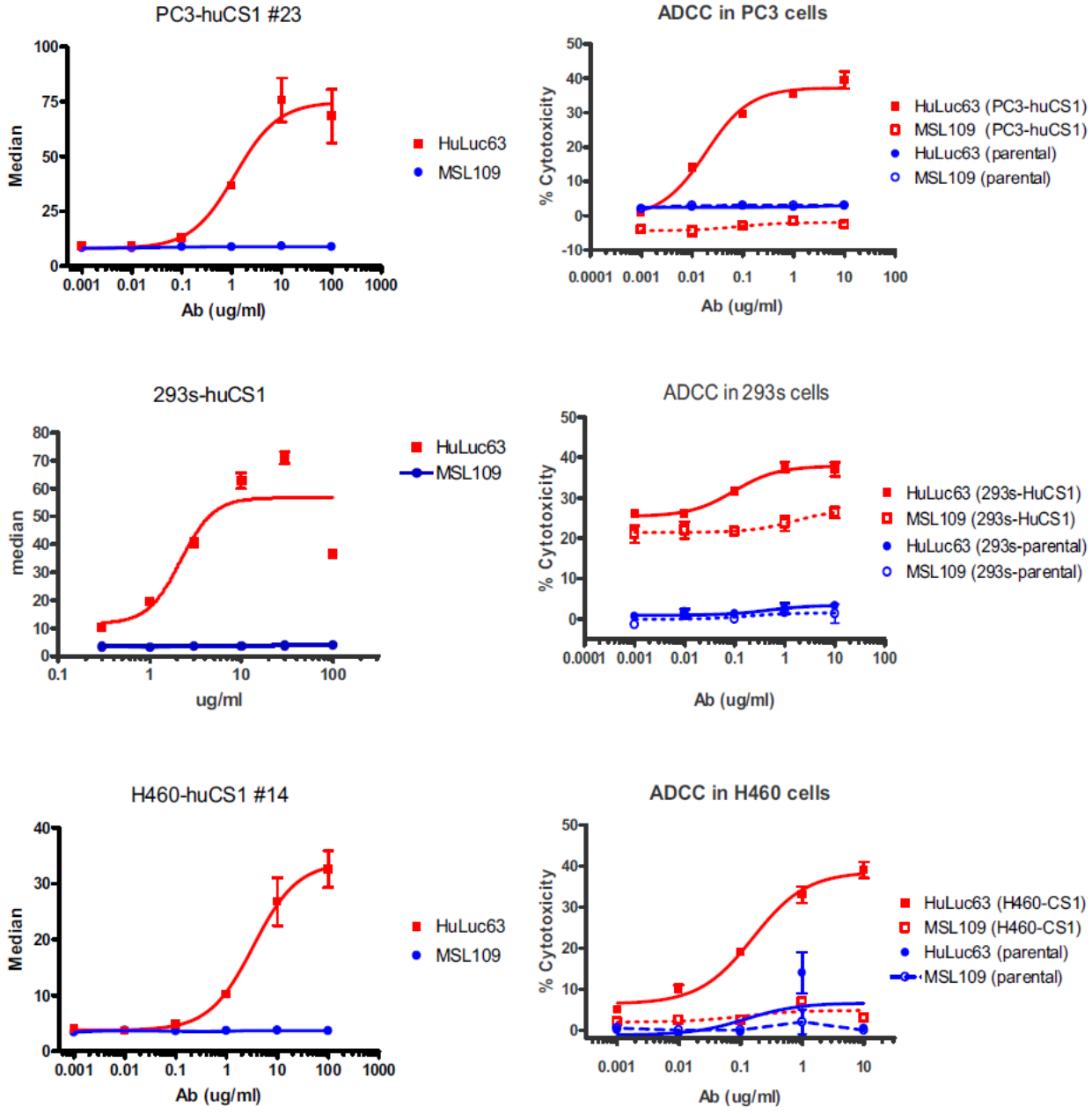
(Figure excerpted from Applicant's submission)



MSL109 = isotype control antibody

Figure 8: Binding of HuLuc63 and mediation of ADCC in cells transfected with cDNA encoding SLAMF7

(Figure excerpted from Applicant's submission)

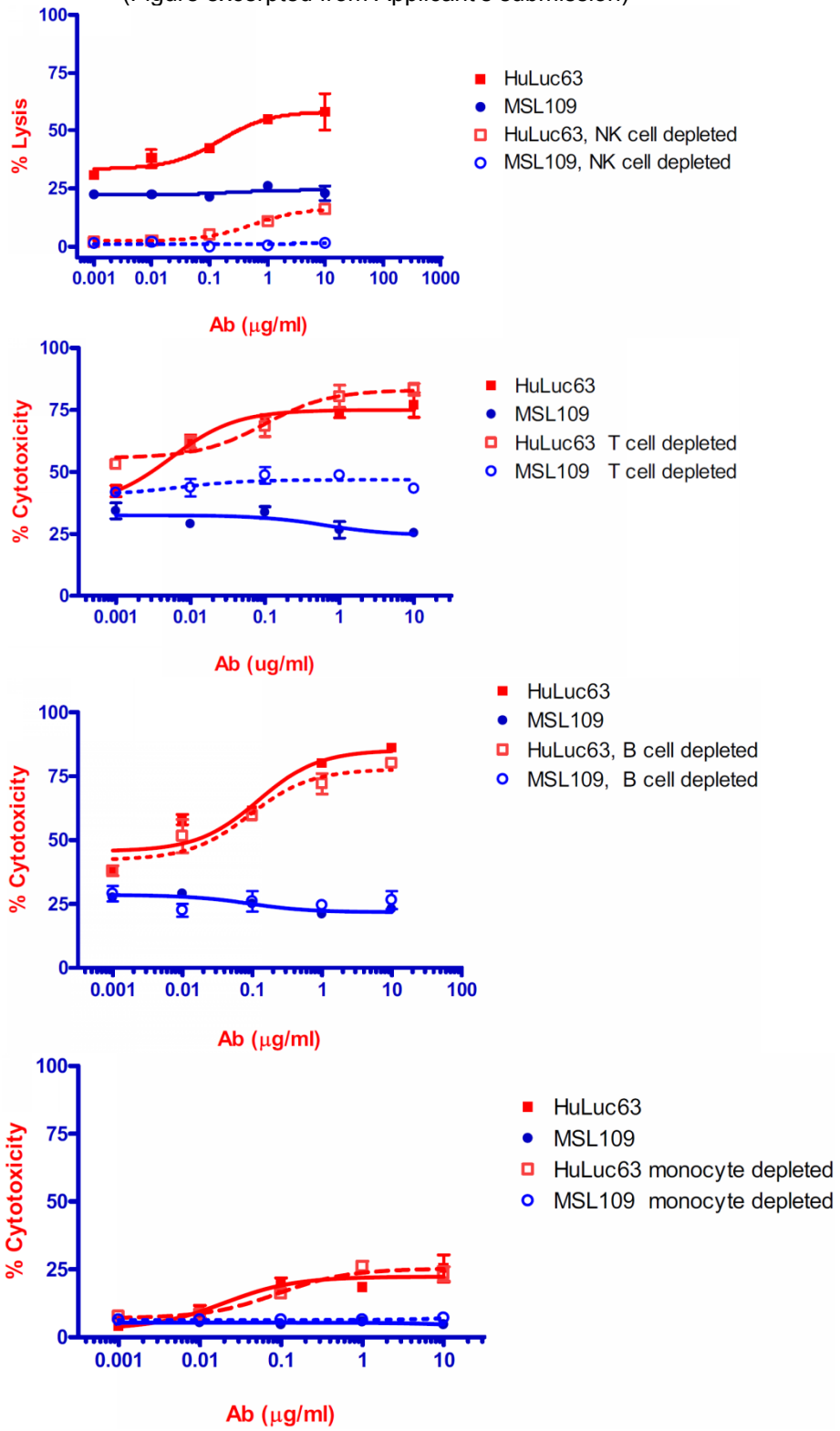


MSL109 = isotype control antibody

Binding of HuLuc63 or isotype control antibody to cell lines expressing recombinant SLAMF7 are shown on the left (parental cell lines not shown). ADCC mediated by HuLuc63 or isotype control antibody in cell lines expressing recombinant SLAMF7 and parental cell lines are shown on the right.

Figure 9: The effect of specific leukocyte depletion on HuLuc63-mediated ADCC in the L363 cell line

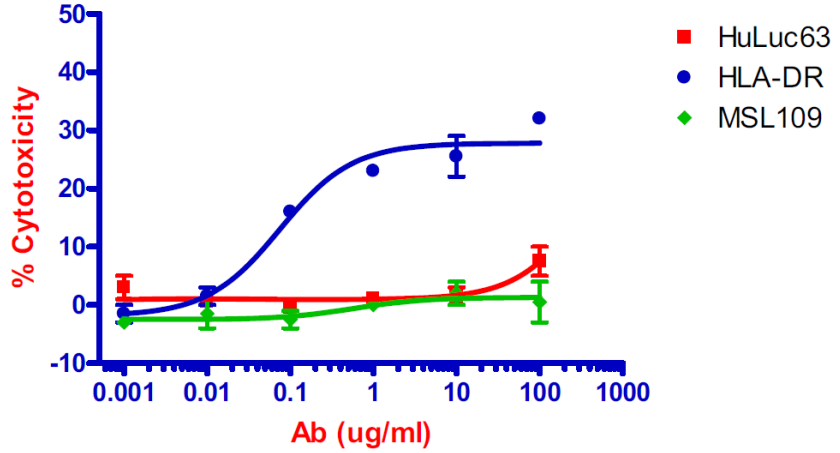
(Figure excerpted from Applicant's submission)



MSL109 = isotype control antibody

Figure 10: HuLuc63-mediated complement-dependent cytotoxicity in the L363 cell line

(Figure excerpted from Applicant's submission)



MSL109 = isotype control antibody; HLA-DR = positive control antibody with known CDC activity

Study title: Elotuzumab directly enhances NK cell cytotoxicity against myeloma via CS1 ligation: evidence for augmented NK cell function complementing ADCC

Collins, SM, Bakan, CE, Swartzel, GD, Hofmeister, CC, Efebera, YA, Kwon, H, Starling, GC, Ciarlariello, D, Bhaskar, S, Briercheck, EL, Hughes, T, Yu, J, Rice, A, and DM Benson, 2013, Elotuzumab directly enhances NK cell cytotoxicity against myeloma via CS1 ligation: evidence for augmented NK cell function complementing ADCC, Cancer Immunol Immunother, 62:1841–1849.

The objective of the study was to explore additional mechanisms by which elotuzumab promotes anti-tumor activity. In vitro studies were conducted to monitor NK cell activation and cytokine production. Results from this study were intended to support the ongoing clinical development of elotuzumab.

Results and Conclusions

- Elotuzumab increased the percentage of normal healthy donor and multiple myeloma patient NK cells expressing the activation marker CD69 and the intensity of CD69 expression (see Figure 11). NK cell activation was also observed with an elotuzumab variant with reduced Fc receptor binding (elo-G2M3) and elotuzumab $F(ab')_2$, indicating NK cell activation was independent of the elotuzumab Fc domain.
- Elotuzumab increased IFN-γ production by NK cells against the L363 multiple myeloma cell line (see Figure 12).
- Elotuzumab caused NK cell degranulation as observed by increased CD107a expression in freshly isolated bone marrow aspirates from patients with multiple myeloma (see Figure 13).
- Elotuzumab directly activates NK cells independent of the Fc portion of the antibody.

Figure 11: Activation of normal healthy donor and multiple myeloma patient NK cells by elotuzumab and elotuzumab variants

(Figure excerpted from Collins et al.)

Figure 12: Production of IFN-γ by NK cells in response to elotuzumab

(Figure excerpted from Collins et al.)

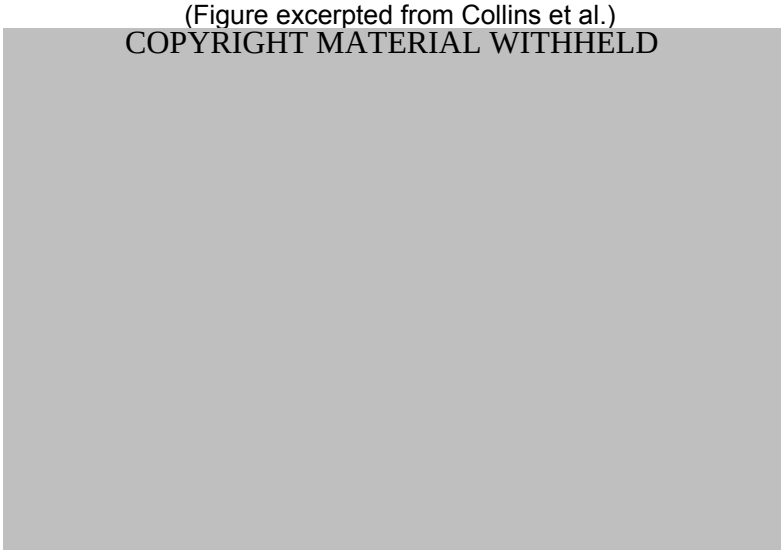
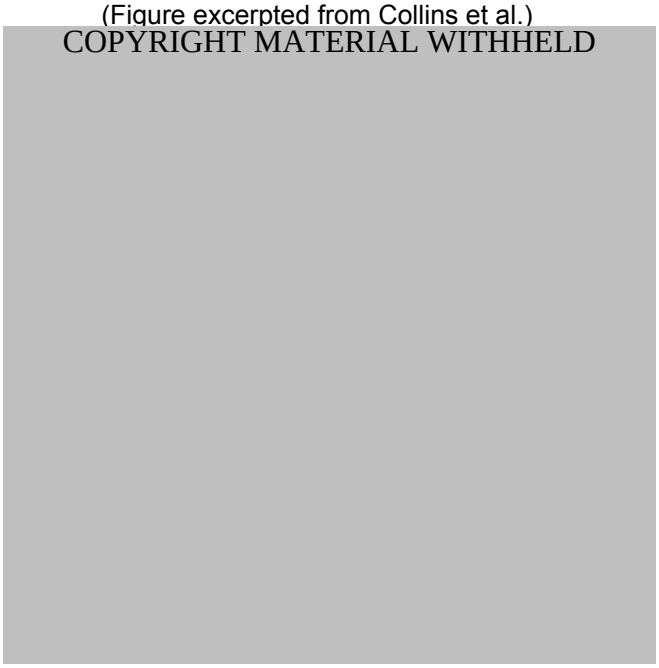


Figure 13: Increased CD107a expression in NK cells in response to elotuzumab

(Figure excerpted from Collins et al.)



Study title: In Vivo Anti-Tumor Efficacy of MuLuc63 and Its Humanized Version, HuLuc63

Study no.:	RTR14
Report date:	May 12, 2006
Study report location:	eCTD 4.2.1.1.
Conducting laboratory:	PDL BioPharma Inc. 34801 Campus Dr. Fremont, CA 94555
GLP compliance:	No

The objectives of the study were to define and compare the in vivo anti-tumor activities of MuLuc63 and its humanized counterpart HuLuc63 (elotuzumab). The anti-tumor activities of MuLuc63 and HuLuc63 were studied in xenograft mouse models with tumors grown from the human multiple myeloma cell lines L363 and OPM2.

Results and Conclusions

- MuLuc63 exhibited dose-dependent anti-tumor activity over the 1 – 10 mg/kg dose range, resulting in decrease in tumor size or tumor eradication (see Figure 14).
- MuLuc63 was significantly more potent than HuLuc63 at the 10 mg/kg dose level (see Figure 15).
- The difference in anti-tumor activity between MuLuc63 and HuLuc63 was attributed to increased ADCC mediated by MuLuc63 as murine NK cells interact more efficiently with the Fc region of MuLuc63 than HuLuc63.

Figure 14: Dose-dependent anti-tumor activity mediated by MuLuc63 in mice with L363 xenografts

(Figure excerpted from Applicant's submission)

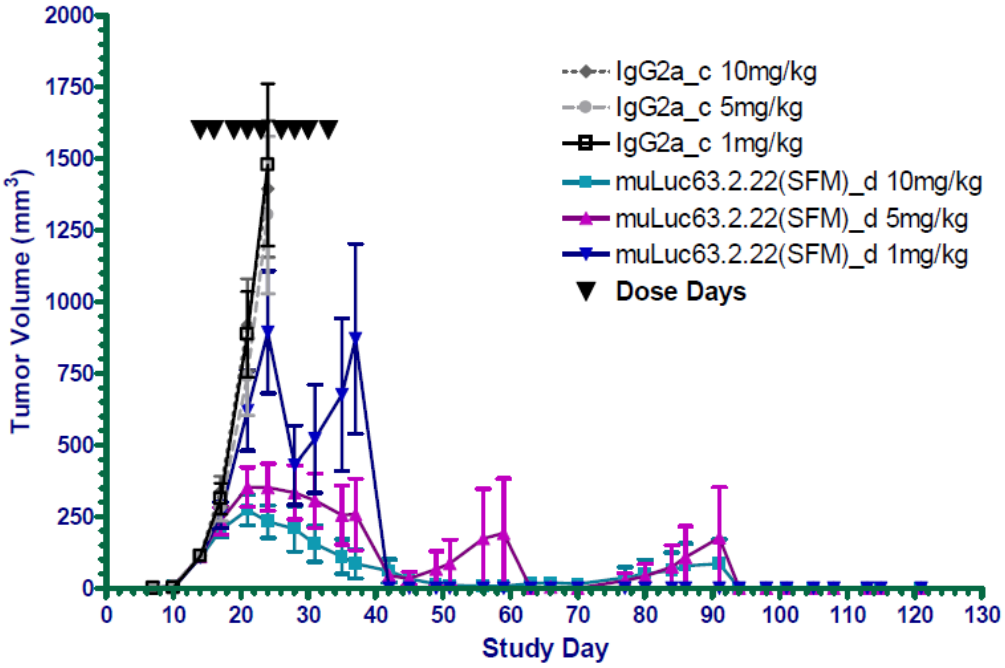
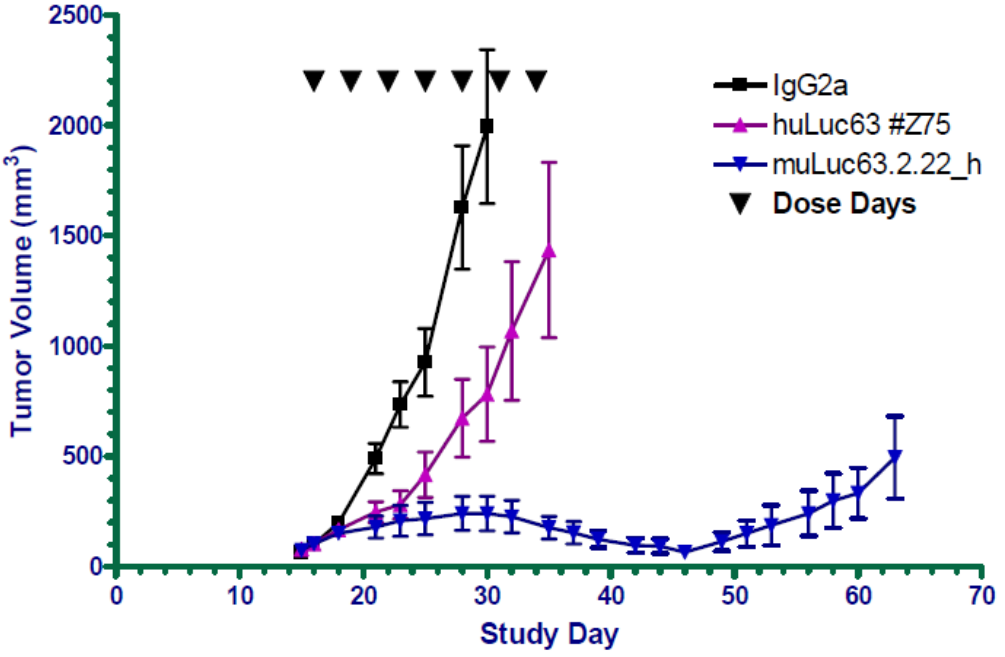


Figure 15: Comparison of anti-tumor activity mediated by MuLuc63 and HuLuc63 in mice with L363 xenografts

(Figure excerpted from Applicant's submission)



(MuLuc63 and HuLuc63 were both dosed at the 10 mg/kg dose level)

Study title: Increased Anti-Tumor Activity of HuLuc63 in Combination with Bortezomib in the OPM-2 Xenograft Model

Study no.:	RTR26
Report date:	December 20, 2007
Study report location:	eCTD 4.2.1.1.
Conducting laboratory:	PDL BioPharma Inc. 34801 Campus Dr. Fremont, CA 94555
GLP compliance:	No

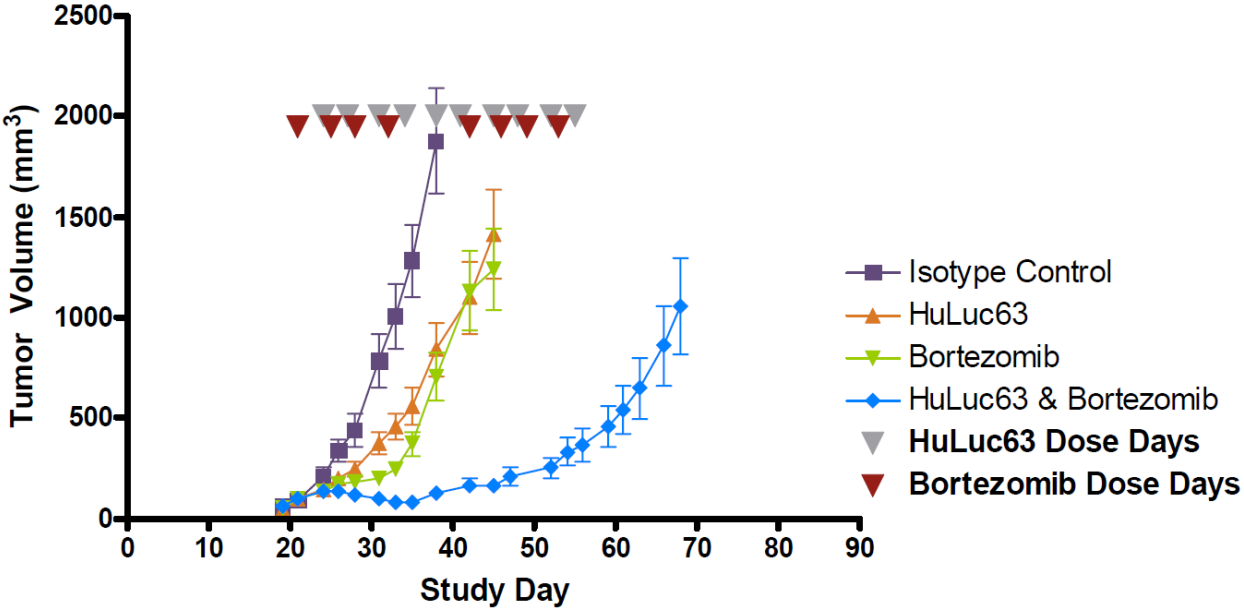
The objective of the study was to investigate whether the combination of HuLuc63 and bortezomib resulted in enhanced anti-tumor activity in the OPM2 xenograft mouse model. (b) (4)

Results and Conclusions

- Significant inhibition of tumor growth was observed in mice that were intraperitoneally administered the combination of HuLuc63 (1 mg/kg twice weekly for 5 weeks) and bortezomib (1 mg/kg twice weekly for 2 weeks, 1 week rest, then twice weekly for 2 more weeks), compared to mice that were administered HuLuc63 or bortezomib monotherapy, or control IgG (see Figure 16).
- The dose of HuLuc63 administered was considered a sub-optimal dose such that single-agent HuLuc63 would result in partial tumor growth inhibition, thus creating a window to monitor further growth inhibition mediated by combination with bortezomib.
- Modest inhibition of tumor growth was observed in mice that were administered HuLuc63 or bortezomib, compared to human IgG1 isotype control antibody.
- Approximately half way through the study, mice in the combination treatment group exhibited 80-85% smaller tumors than mice in the HuLuc63 or bortezomib monotherapy treatment groups.
- In the mice that were administered the combination of HuLuc63 and bortezomib tumors began to grow after the end of treatment. By the end of the study tumors were approximately 1000 mm^3.
- Bortezomib enhances the anti-tumor activity of HuLuc63 in a xenograft mouse model, however tumors expand rapidly upon cessation of therapy.

Figure 16: Effect of HuLuc63 and/or bortezomib on tumor growth in the OPM2 xenograft mouse model

(Figure excerpted from Applicant's submission)



Study title: Elotuzumab enhances natural killer cell activation and myeloma cell killing through interleukin-2 and TNF-α pathways

Balasa, B, Yun, R, Belmar, NA, Fox, M, Chao, DT, Robbins, MD, Starling, GC, and AG Rice, 2015, Elotuzumab enhances natural killer cell activation and myeloma cell killing through interleukin-2 and TNF-α pathways, Cancer Immunol Immunother, 64:61–73.

The objective of the study was to explore the mechanisms by which the anti-tumor activity of elotuzumab was enhanced by lenalidomide. The elotuzumab and lenalidomide combination was studied in an in vitro PBMC and myeloma cell co-culture model and in a xenograft mouse model with tumors grown from the human multiple myeloma cell line OPM2. Results from this study were intended to support ongoing Phase III clinical trials in patients with relapsed/refractory or newly-diagnosed multiple myeloma.

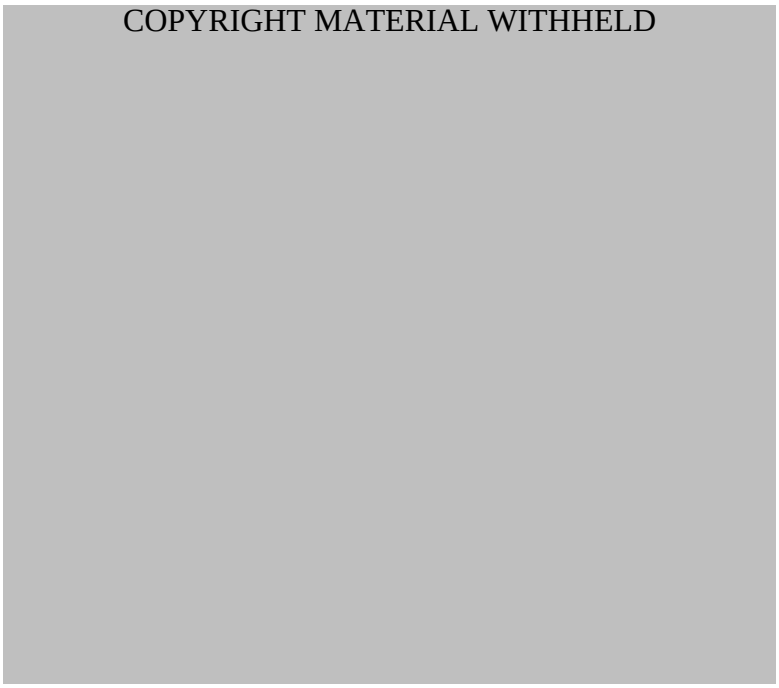
Results and Conclusions

- In vitro, the combination of elotuzumab and lenalidomide resulted in increased levels of TNF-α which contributed to NK cell activation and myeloma cell killing.
- A significant increase in anti-tumor activity was observed in mice that were intraperitoneally administered the combination of elotuzumab (1 mg/kg twice weekly for 3 weeks) and lenalidomide (50 mg/kg/day at 5 days/week), compared to mice that were administered elotuzumab or lenalidomide monotherapy, or control IgG (see Figure 17).

- Similar inhibition of tumor growth was observed in mice that were administered elotuzumab or lenalidomide, compared to human IgG1 isotype control antibody.
- Elotuzumab was administered at a sub-optimal dose such that single-agent elotuzumab resulted in modest inhibition of tumor growth, thus creating a window to observe additional anti-tumor activity mediated by combination with lenalidomide.
- In mice that were administered control IgG, tumors were >1000 mm^3 by Day 42, while tumors in mice that were administered the elotuzumab and lenalidomide combination were <100 mm^3 by Day 42.
- Lenalidomide enhances the anti-myeloma activity of elotuzumab in co-culture experiments and in the OPM2 xenograft mouse model.

Figure 17: Effect of elotuzumab and/or lenalidomide on tumor growth in the OPM2 xenograft mouse model

(Figure excerpted from Balasa et al.)



5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Study title: Determination of Minimal and Optimal Serum Levels of HuLuc63 Required for In Vivo Anti-Tumor Efficacy in a Mouse Xenograft Model

Study no.:	RTR15
Report date:	May 12, 2006
Study report location:	eCTD 4.2.1.1.
Conducting laboratory:	PDL BioPharma Inc. 34801 Campus Dr. Fremont, CA 94555
GLP compliance:	No

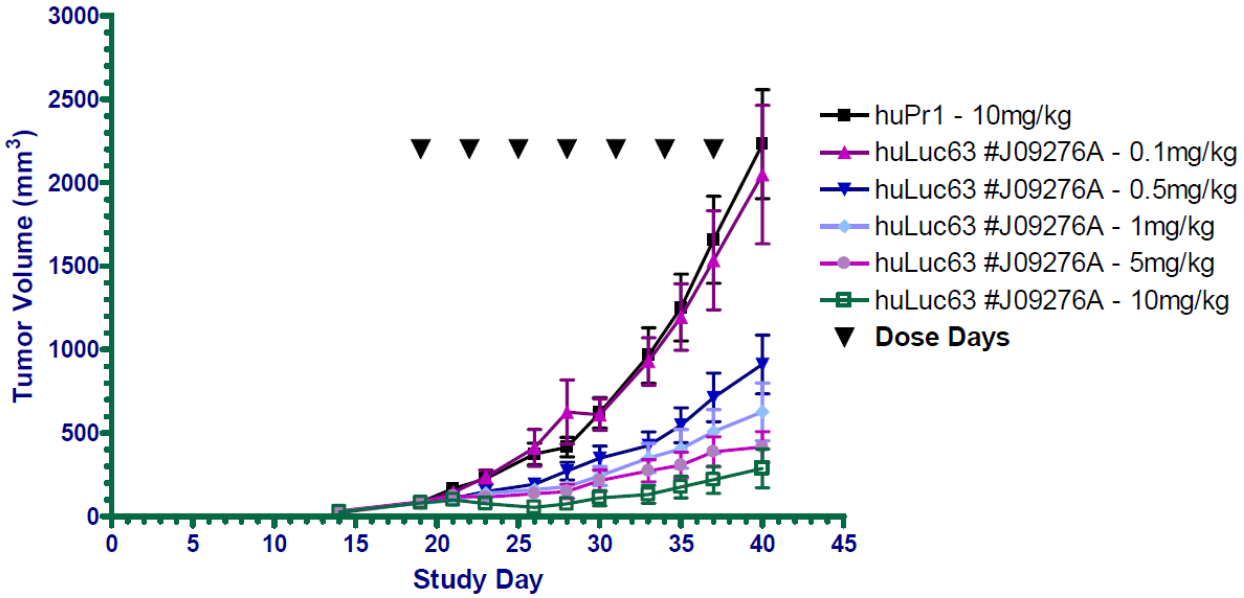
The objectives of the study were to examine the in vivo dose response characteristics of HuLuc63 and to determine the minimal and optimal serum levels of HuLuc63 required for anti-tumor activity.

Results and Conclusions

- SCID mice bearing OPM2 tumors were intraperitoneally administered 0.1, 0.5, 1, 5, or 10 mg/kg HuLuc63 or isotype control antibody once every 3 days for a total of 7 doses. HuLuc63 exhibited significant anti-tumor activity in all dose groups except for the 0.1 mg/kg dose group (see Figure 18). Anti-tumor activity was dose-dependent with maximal anti-tumor activity observed in the 10 mg/kg dose group.
- In the 0.5 mg/kg dose group, minimal and maximal HuLuc63 serum concentrations were 2 µg/mL and 13 µg/mL, respectively (see Table 10). This range of concentrations demonstrates the serum level of HuLuc63 for minimal anti-tumor activity.
- In the 10 mg/kg dose group, minimal and maximal HuLuc63 serum concentrations were 70 µg/mL and 430 µg/mL, respectively. This range of concentrations demonstrates the serum level of HuLuc63 associated with maximal anti-tumor activity.

Figure 18: HuLuc63 dose range finding study with the OPM2 xenograft mouse model

(Figure excerpted from Applicant's submission)



huPr1 = isotype control antibody

Table 10: Mean HuLuc63 serum concentrations after intraperitoneal injection of HuLuc63 into SCID mice bearing OPM2 tumors

Dose group (mg/kg)	$C1_{max}$ (µg/mL)	$C1_{min}$ (µg/mL)	$C6_{min}$ (µg/mL)	$C7_{max}$ (µg/mL)	Terminal (µg/mL)
Placebo	ND	ND	ND	ND	ND
0.1	0.48	0.13	0.43	0.87	0.30
0.5 *	3.55	1.88	6.90	13.02	7.05
1	8.25	3.15	18.90	23.84	13.95
5	43.08	34.03	126.99	175.97	108.91
10 ***	97.98	68.51	272.11	429.08	257.38

$C1_{max}$ = 8 hours after the first dose
$C1_{min}$ = immediately before the second dose
$C6_{min}$ = immediately before the seventh dose
$C7_{max}$ = 8 hours after the last dose
Terminal = one dose-interval after the last dose
ND = none detected
* = Dose at which minimal biological activity was observed
*** = Dose at which maximal biological activity was observed

5.2 Toxicokinetics

The toxicokinetics of elotuzumab are reviewed with study TR07150 under section 6.1.

6 General Toxicology

6.1 Single-Dose Toxicity

Study title: Single Dose Intravenous Infusion Toxicity and Toxicokinetics Study with HuLuc63 in Rhesus Monkeys

Study no.:	TR07150
Study report location:	eCTD 4.2.3.1.
Conducting laboratory and location:	(b) (4)
Date of study initiation:	September 2, 2005
GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	HuLuc63, lot # J09276A, purity: 99.7%

Key Study Findings:

- A single dose of intravenously infused HuLuc63 was well tolerated in rhesus monkeys with no observed mortality, clinical signs, or test article related changes in clinical pathology parameters.
- HuLuc63 toxicokinetics appear to be linear within the 30 mg/kg to 100 mg/kg dose range and fit a two-compartment model. HuLuc63 exhibited a half-life of 8-15 days. The potential for immunogenicity was not directly assessed, but an abrupt reduction in HuLuc63 serum concentrations after Day 21 suggested an immunogenic response had occurred.
- HuLuc63 is directed against human SLAMF7 and does not cross-react with SLAMF7 in the rhesus monkey or any other non-human species. This exploratory toxicity and toxicokinetic study in the rhesus monkey only provides a limited evaluation of the off-target effects and toxicokinetics of HuLuc63.

An exploratory non-GLP single-dose toxicity and toxicokinetic study was conducted in rhesus monkeys. HuLuc63 binds human SLAMF7 and does not cross-react with any non-human tissue. Preliminary data suggested HuLuc63 bound rhesus monkey peripheral blood B cells, however this binding was not reproducible and rhesus monkeys are not considered a relevant species for toxicity studies. The current study provides a limited evaluation of the off-target effects and toxicokinetics of HuLuc63.

Male or female rhesus monkeys (1/sex/group) were intravenously infused with 0, 30, or 100 mg/kg HuLuc63. The proposed clinical route of administration is also intravenous infusion. The high dose of 100 mg/kg corresponds to an exposure approximately 8-fold higher than that observed in humans at the recommended dose of 10 mg/kg. Monkeys were observed for 44 days before scheduled euthanasia on Day 45.

Methods

Doses:	0 (vehicle control), 30, or 100 mg/kg/day
Frequency of dosing:	Single dose, followed by a 44 day observation period
Route of administration:	Intravenous infusion (30 minute duration) through a vascular access port to a jugular catheter
Dose volume:	10 mL/kg
Formulation/Vehicle:	20 mM sodium citrate, 120 mM sodium chloride, 0.05% Tween 80, pH=6
Species/Strain:	Rhesus monkey (*Macaca mulatta*)
Number/Sex/Group:	1/sex/group
Age:	4 to 6 years old at initiation of treatment
Weight:	Males: 4.2 to 6.8 kg at initiation of treatment Females: 3.9 to 5.4 kg at initiation of treatment
Satellite groups:	No
Unique study design:	No
Deviation from study protocol:	No

Observations and times:

Mortality and clinical signs:	- Twice daily
Detailed physical examination:	- Once during the predose phase - Before dosing on Day 1 - Weekly thereafter - Before sacrifice
Cageside observations:	- 2 and 4 hours postdose - Once daily on nondose days
Body weights:	- Once during the predose phase - Before dosing on Day 1 - Weekly thereafter
Qualitative food consumption:	- Daily
Clinical chemistry:	- Once during the predose phase - Day 3 - At scheduled sacrifice
Urinalysis:	- Once during the predose phase - Day 3 - At scheduled sacrifice
Hematology:	- Once during the predose phase - Day 3 - At scheduled sacrifice
Toxicokinetics / immunogenicity:	- Immediately before infusion on Day 1 - 1, 2, 4, 8, 24 and 72 hours postdose - Once on Days 8, 15, 22, 36, and 43

Peripheral blood immunopheno-typing:	- Once prior to catheterization - Once during the predose phase prior to randomization on Day -7 - On Day 1 at -1, 24, and 72 hours postdose - On Days 8, 15, 22, 36, and 43
Lymphocyte count immunopheno-typing:	- Once prior to catheterization - Once during the predose phase prior to randomization on Day -7 - On Day 1 at -1, 24, and 72 hours postdose - On Days 8, 15, 22, 36, and 43
Sacrifice and necropsy:	- Day 45

Mortality

Unremarkable

Clinical signs and detailed physical examination

Unremarkable

Body weights

Unremarkable

Qualitative food consumption

Unremarkable

Clinical chemistry

Decreases in total protein, albumin and calcium on Day 3, relative to predose levels, were observed in both control and treated animals, and were considered to be the result of blood lost from the multiple samples collected for toxicokinetic and immunophenotyping evaluations.

Urinalysis

Unremarkable

Hematology

Decreases in erythrocyte count, hemoglobin and hematocrit on Day 3, relative to predose levels, were observed in both control and treated animals, and were considered to be the result of blood lost from the multiple samples collected for toxicokinetic and immunophenotyping evaluations.

Toxicokinetics / immunogenicity

HuLuc63 toxicokinetics appear to be dose-independent (linear) within the dose range tested and fit a two-compartment model (see Table 11). The observed HuLuc63 half-life was 8-15 days.

Toxicokinetic parameters in rhesus monkeys are of questionable relevance to humans as HuLuc63 does not cross-react with any tissues in rhesus monkeys.

The potential for immunogenicity was not directly addressed. The study authors cite an abrupt reduction in HuLuc63 serum concentrations after Day 21, and postulate an immunogenic response to be the cause. Due to the aforementioned reduction in HuLuc63 serum concentrations after Day 21, serum concentrations from Days 36 and 43 were excluded from the final toxicokinetic analysis.

Table 11: Toxicokinetics of a single dose of HuLuc63 in rhesus monkeys

Group	Dose (mg/kg)	C_{max} (µg/mL)	t_{max} (hr)	$AUC_{0\text{-}inf}$ (hr*mg/mL)	Half-life (days)	CL (mL/hr/kg)	V_t (mL/kg)
2 (n=2)	30	640,644	1.00	118, 194	8.0,14.8	0.155, 0.254	46.3, 46.4
3 (n=2)	100	1657,2065	2.00, 8.00	335, 447	8.4, 9.7	0.224, 0.299	49.9, 61.5
Mean	---	---	3.00	---	10.2	0.233	51.0
SD	---	---	3.37	---	3.12	0.0604	7.17
CV (%)	---	---	112	---	30.5	26	14.1

Reported data was the range of lowest to highest values.
Sample size = 2/group
SD = standard deviation, CV(%) = coefficient of variation

Peripheral blood immunophenotyping

Unremarkable

Lymphocyte count immunophenotyping

Unremarkable

Sacrifice and necropsy

Unremarkable

Gross pathology

Unremarkable

Organ weights

Unremarkable

Histopathology

All tissues in Table 12 were processed, preserved in 10% neutral-buffered formalin, and examined microscopically.

Adequate Battery: Yes

Peer Review: No

Histological Findings:

Microscopic findings including slight to moderate fibrosis at the infusion site, slight to minimal proliferation at the infusion site, and slight to moderate chronic inflammation at the catheter site were observed in most dose groups. These findings were considered normal for use with short-term indwelling intravenous catheters.

The remaining microscopic findings are commonly encountered in toxicity studies conducted in rhesus monkeys, were generally distributed randomly between dose groups, and thus were considered unrelated to HuLuc63.

Table 12: Histopathology inventory, single dose toxicity and toxicokinetic study in rhesus monkeys

Adrenal, Cortex	Lung
Adrenal, Medulla	Mammary, Female
Aorta	Marrow, Femur
Bone, Femur	Marrow, Sternum
Bone, Sternum	Muscle, Bi Fem
Brain	Nerve, Optic
Catheter Site	Nerve, Sciatic
Cecum	Ovary
Cervix	Pancreas
Colon	Parathyroid
Duodenum	Pituitary
Esophagus	Rectum
Eye	Skin
Gallbladder	Spinal Cord
GI, Lacrimal	Spleen
GI, Mandib Saliv	Stomach, GI
Heart	Thymus
Ileum	Thyroid
Infusion Site	Tongue
Jejunum	Trachea
Kidney	Urinary Bladder
Liver	Uterus

LN, Mesenteric	Vagina
LN, Mandibular	

*Inguinal lymph nodes and tonsil were not collected

Dosing Solution Analysis

HuLuc63 dose formulations were within ±10% of their respective target concentrations, which met the protocol requirements. The concentration of the HuLuc63 stability samples after 8 hours at room temperature were within ±10% of their respective target concentrations.

6.2 Repeat-Dose Toxicity

Repeat-dose toxicity studies of elotuzumab were not conducted due to the lack of a relevant toxicology species or a valid transgenic mouse model.

7 Genetic Toxicology

No genetic toxicology studies were conducted. Genetic toxicology studies are generally not necessary to support marketing of biotechnology-derived pharmaceuticals such as elotuzumab as discussed in the ICH S6 guidance document.

8 Carcinogenicity

No carcinogenicity studies were conducted. Carcinogenicity studies are not necessary to support the marketing of therapeutics intended to treat patients with advanced cancer as discussed in the ICH S9 guidance document

9 Reproductive and Developmental Toxicology

No reproductive and developmental toxicology studies were conducted due to the lack of a pharmacologically-relevant animal species. The Applicant submitted a risk assessment for the potential for reproductive and developmental toxicity for elotuzumab based on tissue distribution of SLAMF7 and published literature. SLAMF7 is not expressed on cells in the reproductive organs with the exception of plasma cells and immunoblasts in the uterus and cervix. It is not known whether binding of elotuzumab to plasma cells and immunoblasts in these reproductive organs affects reproduction in vivo. Elotuzumab is an IgG1 monoclonal antibody which has the potential to cross the placental barrier permitting direct fetal exposure. The impact of elotuzumab on fetal development is unknown, however published reports indicate SLAMF7-deficient mice appear healthy suggesting SLAMF7 does not play a role in embryo-fetal development.

10 Special Toxicology Studies

Study title: Final Immunopathology Report Cross-Reactivity of HuLuc63 with Normal Human Tissues

Study no.:	TR06051
Study report location:	eCTD 4.2.3.7.7.
Conducting laboratory and location:	(b) (4) [redacted]
Date of study initiation:	March 3, 2006
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	HuLuc63, lot # 05CS001A, purity: 99.5%

A GLP-compliant tissue cross-reactivity study was conducted to evaluate the cross-reactivity of HuLuc63 with cryosections of normal human tissues (see Table 13). The staining conditions and concentration of HuLuc63 were determined in a preliminary GLP-compliant method qualification study (study not reviewed). HuLuc63 was applied to human tissue sections (three or more normal human donors per tissue) at two concentrations (3 µg/mL and 10 µg/mL). Cryosections of normal human tonsil and colon were used as positive control tissues and normal human cerebellum and kidney served as negative control tissues. Additional controls included the substitution of HuLuc63 with irrelevant human IgG1 (negative control) and omission of HuLuc63 (assay control). Positive tissue staining control was accomplished by staining for the presence of β_2-microglobulin in replicate sections of all tissues examined. Binding of the antibodies to the test or control tissues was detected by an indirect immunoperoxidase procedure with tyramide-signal amplification. Stained tissue slides were read by the Study Pathologist to identify the tissue or cell type stained and the intensity of staining (graded ± [equivocal], 1+ [weak], 2+ [moderate], 3+ [strong], 4+ [intense], or Neg [negative]). The overall reaction sequence for immunoperoxidase staining is in Table 14.

Table 13: Normal human tissues examined for HuLuc63 cross-reactivity (three or more donors per tissue)

Adrenal
Blood cells (granulocytes, lymphocytes, monocytes, platelets)
Blood vessels (endothelium)
Bone marrow
Brain (cerebrum [cortex], cerebellum)
Breast (mammary gland)
Eye
Gastrointestinal tract (colon [large intestine], esophagus, small intestine, stomach)
Heart
Kidney (glomerulus, tubule)
Liver

Lung
Lymph node
Ovary and fallopian tube (oviduct)
Pancreas
Parathyroid
Peripheral nerve
Pituitary
Placenta
Prostate
Salivary gland
Skin
Spinal cord
Spleen
Striated (skeletal) muscle
Testis
Thymus
Thyroid
Tonsil
Ureter
Urinary bladder
Uterus (body [endometrium], cervix)

Table 14: The overall reaction sequence for immunoperoxidase staining

Primary antibody		**Secondary antibody + biotin precomplex**	**Human gamma globulins**	**DAB+**
HuLuc63	3 µg/mL	6 µg/mL	3 µg/mL	✓
	10 µg/mL	10 µg/mL	10 µg/mL	✓
Human IgG1	3 µg/mL	6 µg/mL	3 µg/mL	✓
	10 µg/mL	10 µg/mL	10 µg/mL	✓
None	---	---	10 µg/mL	✓

Results and Conclusions

HuLuc63 specifically stained the positive control tissue sections with strong intensity indicating high affinity binding. Staining was consistent and reproducible at the lower concentration of HuLuc63 (3 µg/mL). At the higher concentration of HuLuc63 (10 µg/mL) staining was more variable which was judged to represent either anatomic differences or technical issues with the staining procedure. HuLuc63 did not specifically react with either negative control material. The negative control antibody (human IgG1 with unspecified antigenic specificity) did not react with either positive control or negative control materials. Overall, the assay was observed to be sensitive, specific, and reproducible.

HuLuc63 reacted with the membrane and/or cytoplasm of plasma cells and/or immunoblasts in the bone marrow, breast, cervix, esophagus, Fallopian tube, gastrointestinal tract, liver, lymph node, pancreas, salivary gland, small intestine, spleen, stomach, thymus, thyroid, tonsil, ureter, and uterus. Staining of plasma cells and immunoblasts was expected as HuLuc63 is directed against SLAMF7, an epitope expressed by plasma cells and immunoblasts. No specific cross-reactivity was observed with any other tissue element in any of the tissues examined. The results of this study indicate that HuLuc63 stained only plasma cells and/or immunoblasts in the normal human tissue panel and that there was no unexpected tissue binding or cross-reactivity attributable to HuLuc63.

Study title: Local Tolerance Study in Rabbits (Intravenous Injection) with HuLuc63

Study no.:	TR06050
Study report location:	eCTD 4.2.3.6.
Conducting laboratory and location:	(b) (4)
Date of study initiation:	February 20, 2006
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	HuLuc63, lot # 05CS001A, purity: 99.5%

A GLP-compliant study was conducted to evaluate the local tolerance of HuLuc63 when administered as a single dose by intravenous injection in rabbits. Six female New Zealand white rabbits were assigned to a single-dose group of 5 mg HuLuc63. HuLuc63 (1.0 mL/site at a concentration of 5 mg/mL) or vehicle control (20 mM sodium citrate, 120 mM sodium chloride, 0.05% Tween 80, pH=6.05) was administered into the right marginal ear vein and left marginal ear vein, respectively. Following administration of HuLuc63, two rabbits were euthanized and subjected to a specialized necropsy each at 30 minutes, 3 hours, and 24 hours postdose. The injection site was examined macroscopically and scored for observations of erythema and edema. The injection sites and the surrounding tissues were removed, processed, and examined microscopically.

Results and Conclusions

All rabbits survived to scheduled sacrifice with no clinical observations. No macroscopically visible erythema or edema were present in any animal predose or at any time point following administration of HuLuc63. The microscopic observations of hemorrhage, vessel wall disruption, heterophil infiltrate and collagen degeneration in both ears were primarily minimal in severity and were likely the result of the injection procedure and not related to HuLuc63. HuLuc63 appears to present little risk of a significant adverse reaction when administered by intravenous injection.

Study title: In vitro cytokine analysis of elotuzumab-treated primary immune cells

Study no.:	R&D/14/0759
Report date:	October 28, 2014
Study report location:	eCTD 5.3.1.4.
Conducting laboratory:	AbbVie Biotherapeutics Inc. (formerly PDL BioPharma Inc.) 34801 Campus Dr. Fremont, CA 94555
GLP compliance:	No

The objective of the study was to assess the impact of elotuzumab on the release of cytokines from human immune cells in vitro. Elotuzumab (20 µg/mL) or control antibody was incubated with human whole blood samples from 20 healthy donors for 24 hours at 37ºC. Samples were centrifuged and the plasma supernatants were analyzed for the levels of 22 cytokines (see Table 15) with a Beadlyte® Human 22-plex Beadmaster kit following the manufacturer's instructions.

Table 15: Cytokines examined after incubation of elotuzumab with whole blood from normal human donors

IL-1α	IL-8	IFNγ
IL-1β	IL-10	IP-10
IL-2	IL-12(p40)	MCP-1
IL-3	IL-12(p70)	MIP-1α
IL-4	IL-13	RANTES
IL-5	IL-15	TNFα
IL-6	Eotaxin	
IL-7	GM-CSF	

Results and Conclusions

- Elotuzumab treatment caused statistically elevated levels of 10 of 22 cytokines, compared to control IgG (see Table 16).
- The number of donors with statistically significant ≥2-fold elevated cytokine levels ranged from 3 (IL-2 and MIP-1α) to 19 (IP-10).
- The fold increase in levels for some cytokines was large and significant (e.g. IL-6), but the absolute levels were low, possibly below a clinically meaningful level.
- Elotuzumab had no significant impact on the levels of 9 cytokines tested.
- For both elotuzumab and control IgG, levels of 3 cytokines were below the limit of detection.

Table 16: Cytokines levels observed after incubation of elotuzumab with whole blood from normal human donors

Cytokine	IgG control mean ± SD (pg/mL)	Elotuzumab mean ± SD (pg/mL)	# of donors ≥ 2-fold increase	P value
IL-6	3.6±8.1	27.3±31.7	10	0.002
IP-10	201±306	2564±3211	19	0.002
MCP-1	277±288	4844±6818	17	0.003
IL-8	207±250	380±326	9	0.005
IFNγ	11.5±16.1	32.8±38.1	9	0.005
TNFα	20.0±30.7	28.3±36.3	7	0.006
IL-12(p40)	200.6±276.8	301.2±382.8	8	0.011
IL-2	11.2±11.4	15.4±14.0	3	0.013
MIP-1α	517±302	671±381	3	0.019
RANTES	1357±1621	2114±2409	5	0.030
IL-15	*13.2±39.0*	*15.1±43.5*	*3*	*0.086*
IL-12(p70)	*2.6±1.7*	*2.3±1.5*	*0*	*0.173*
GM-CSF	*21.9±38.8*	*23.6±37.3*	*6*	*0.227*
Eotaxin	*51.7±54.2*	*54.1±52.5*	*1*	*0.277*
IL-4	*63.9±120*	*67.3±121*	*3*	*0.288*
IL-1β	*34.8±32.8*	*33.8±38.9*	*3*	*0.449*
IL-1α	*753±1313*	*762±1114*	*4*	*0.463*
IL-3	*1.6±1.3*	*1.6±1.1*	*2*	*0.484*
IL-13	*17.2±36.4*	*17.3±34.9*	*1*	*0.484*
IL-5	*0±0*	*0±0*	*n/a*	*n/a*
IL-7	*0±0*	*0±0*	*n/a*	*n/a*
IL-10	*0±0*	*0±0*	*n/a*	*n/a*

Italics = not statistically significant

Study title: Hemolysis Assay in Human Whole Blood with HuLuc63

Study no.:	TR06047
Study report location:	eCTD 4.2.3.7.7.
Conducting laboratory and location:	(b) (4)
Date of study initiation:	February 15, 2006
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	HuLuc63, lot # 05CS001A, purity: 99.5%

A GLP-compliant study was conducted to evaluate the potential for HuLuc63 to induce hemolysis of whole blood from normal human donors. Freshly collected whole blood was incubated with HuLuc63, positive hemolysis control (0.1% sodium carbonate solution), or negative hemolysis control (0.9% sodium chloride solution) for 60 minutes

at 37°C with occasional gentle mixing. Samples were centrifuged and the supernatants were analyzed spectrophotometrically. The degree of hemolysis induced by HuLuc63 was inferred from the optical density of the supernatants at 545 nm, with the negative control and positive control samples scaled to represent 0% and 100% hemolysis, respectively. Observed hemolysis values of >5% were judged to be positive for hemolysis.

Results and Conclusions

- A 10 mg/mL solution of HuLuc63 did not cause hemolysis of human whole blood after an exposure period of 60 minutes at 37ºC (see Table 17).
- The positive and negative control articles performed as expected and the assay was deemed reliable.
- HuLuc63 is not expected to cause hemolytic activity in patients.

Table 17: Hemolysis of human whole blood induced by HuLuc63 or control articles

		Optical density at 545 nm				Hemolysis (%)
Sample description		Replicate 1	Replicate 2	Replicate 3	**Mean**	
Negative control		0.031	0.028	0.027	0.029	0
Positive control		0.912	0.836	0.64	0.796	100
HuLuc63	2 mg/mL	0.027	0.024	0.021	0.024	-0.65
	5 mg/mL	0.02	0.02	0.022	0.021	-1.04
	10 mg/mL	0.019	0.022	0.022	0.021	-1.04

11 Integrated Summary and Safety Evaluation

Elotuzumab mechanism of action and characterization of activity

The Applicant conducted pharmacology studies to characterize the elotuzumab mechanism of action. Elotuzumab bound SLAMF7-expressing multiple myeloma cell lines, reaching saturation at 30 µg/mL, but did not bind cell lines deficient in human SLAMF7. When the cell lines deficient in human SLAMF7 were transfected with cDNA encoding human SLAMF7, elotuzumab bound the cells reaching saturation at 10 µg/mL. In the presence of NK cells, elotuzumab-dependent killing of SLAMF7-expressing cells was observed, however there was no evidence of cytotoxicity in cells lacking SLAMF7 or in the absence of NK cells. Given the antibody-dependent nature of the cell killing, and the requirement for NK cells, the cytotoxic activity of elotuzumab was determined to be at least in part due to antibody-dependent cellular cytotoxicity (ADCC). Elotuzumab also binds SLAMF7 on NK cells causing upregulation of CD69, increased cytokine production, and degranulation, suggesting elotuzumab may also directly activate NK cells. Complement-dependent cytotoxicity (CDC) does not contribute to elotuzumab-mediated cytotoxicity, but other mechanisms of action cannot be definitively excluded.

The in vivo anti-tumor activity of elotuzumab was studied in xenograft mouse models with tumors grown from the human multiple myeloma cell lines L363 and OPM2. Elotuzumab caused dose-dependent anti-tumor activity in all but the lowest dose group tested (0.1 mg/kg). The dose level of elotuzumab at which maximal anti-tumor activity was observed was the highest dose tested (10 mg/kg), which resulted in a serum concentration range of 70 µg/mL (C_{min}) to 430 µg/mL (C_{max}). This dose level resulted in sustained inhibition of tumor growth until cessation of therapy. Human pharmacokinetic studies have determined a mean C_{min} above the target threshold concentration of 70 µg/kg can be achieved at the proposed clinical dose of 10 mg/kg.

Elotuzumab monotherapy provides significant anti-tumor activity in xenograft-bearing mice, however patients do not derive benefit from elotuzumab monotherapy. The anti-tumor activity of elotuzumab was studied in combination with bortezomib or lenalidomide, both of which are commonly used in the management of patients with multiple myeloma. In the xenograft mouse model elotuzumab, bortezomib, and lenalidomide each conferred similar anti-tumor activity, but when elotuzumab was combined with either bortezomib or lenalidomide enhanced anti-tumor activity was observed with no increase in toxicity. (b) (4) the combination studies in mice do support the clinical combination of elotuzumab with (b) (4) lenalidomide.

Elotuzumab binding selectivity and species specificity

The Applicant conducted pharmacology and toxicology studies to evaluate the binding specificity of elotuzumab. Elotuzumab bound purified recombinant human SLAMF7 with an in vitro binding affinity (K_D) of 30 nM to 45 nM, but did not bind to purified recombinant or cell surface expressed SLAMF7 from any nonhuman species tested. The specificity of elotuzumab to human SLAMF7 is remarkable given the SLAMF7 protein is highly conserved among primate species, with >90% sequence identity between the human, chimpanzee, cynomolgus, and rhesus monkey.

Due to the lack of a relevant animal species to conduct toxicity studies, the Applicant conducted a limited toxicological evaluation of elotuzumab which the FDA previously determined to be acceptable. The Applicant conducted a single dose toxicity study of intravenously infused elotuzumab in rhesus monkeys with no clinical findings at the highest dose level tested (100 mg/kg). The high dose level of 100 mg/kg corresponds to an exposure approximately 8-fold higher than that observed in humans at the proposed clinical dose of 10 mg/kg. The immunogenicity of elotuzumab was not directly investigated in this study, but changes in toxicokinetic parameters suggested an immune response had occurred. Given elotuzumab is a humanized antibody an immune response in rhesus monkeys is not unexpected and does not predict the clinical immunogenicity, although 18.5% of the patients treated with elotuzumab did develop anti-drug antibodies. The elotuzumab toxicokinetics were linear within the 30 mg/kg to 100 mg/kg dose range with an observed half-life of 8-15 days. This is in contrast to clinical data that suggests the half-life of elotuzumab, when combined with bortezomib

or lenalidomide, to be 33-43 days. The Applicant provides two possible explanations for the discrepancy; 1) dexamethasone may affect antibody clearance and 2) in patients, elotuzumab has a significant non-linear rate of elimination which confounds the estimation of half-life.

An in vitro cytokine release experiment with human whole blood identified elotuzumab to cause elevated levels of 10 cytokines. Indeed, acute changes in cytokines that manifest as infusion reactions have been observed in clinical studies, and patients should be closely monitored and be premedicated with dexamethasone, H1 blocker, H2 blocker, and acetaminophen. The local tolerance of elotuzumab was studied in rabbits where a single-dose of intravenously infused elotuzumab (5 mg) was well tolerated with no clinical findings. A 10 mg/mL solution of elotuzumab did not cause hemolysis of human whole blood. In summary, elotuzumab appears to present little risk of off-target toxicity or a significant local adverse reaction when administered by intravenous injection.

12 Appendix/Attachments

None

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MICHAEL L MANNING
11/02/2015

CHRISTOPHER M SHETH
11/02/2015