Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for elotuzumab

Proprietary Product Name: Empliciti

Sponsor: Bristol-Myers Squibb Australia Pty Ltd

October 2017

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
ACPM	Advisory Committee on Prescription Medicines
ADA	anti-drug antibody
ADCC	antibody-dependent cellular cytotoxicity
AE	adverse event
AST	aspartate aminotransferase
AUC	area under the serum concentration-time curve
BA	bioavailability
Bd	bortezomib+dexamethasone
BE	bioequivalence
BLA	biologic license application
BMS	Bristol-Myers Squibb
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
Cmax	maximum concentration
CrCl	creatinine clearance
CSR	clinical study report
CYP	cytochrome P450
DDI	drug-drug interactions
DOR	duration of response
DS	drug substance
EBMT	European Group for Blood and Bone Marrow Transplant
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
E-Bd	elotuzumab+bortezomib+dexamethasone
ECL	electrochemiluminescence

Abbreviation	Meaning
E-CTd	elotuzumab + cyclophosphamide + thalidomide + dexamethasone
E-Ld	elotuzumab+lenalidomide+dexamethasone
EMA	European Medicines Agency
E-R	exposure-response
E-Td	elotuzumab+thalidomide +dexamethasone
FDA	US Food and Drug Administration
EBMT	European Group for Blood and Bone Marrow Transplant
ESRD	end-stage renal disease
GFR	glomerular filtration rate
GM-CSF	granulocyte-macrophage colony-stimulating factor
HR	hazard ratio
HSCT	hemopoietic stem cell transplant
IA	interim analysis
ICH	International Conference on Harmonization
IMiD	immunomodulatory drugs
IMWG	International Myeloma Working Group
Ig	immunoglobulin
IR	infusion reaction
IRC	independent review committee
ISS	International Staging System
IV	intravenous
Ld	lenalidomide+dexamethasone
K-M	Kaplan-Meier
LDH	lactate dehydrogenase
mAb	monoclonal antibody

Abbreviation	Meaning
MCP-1	monocyte chemotactic protein
MedDRA	Medical Dictionary for Regulatory Activities
MM	multiple myeloma
MTD	maximum tolerated dose
Nab	neutralizing antibodies
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK	natural killer (cells)
NRF	Normal renal function
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cells
PD	pharmacodynamics
PFS	progression free survival
PGX	pharmacogenomix
PK	pharmacokinetics
PLD	pegylated liposomal doxorubicin
PPK	population pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PO	per os (orally)
P-Y	patient-years
Q2W	every 2 weeks
QD	once daily
SAE	serious adverse event
RI	renal impairment
RO	receptor occupancy

Abbreviation	Meaning
RR	relapsed/refractory
SAP	Statistical Analysis Plan
SCT	stem cell transplant
SCS	Summary of Clinical Safety
SI	International Standard
SLAMF7	Signalling Lymphocyte Activation Molecule Family 7
SMQ	standardized MedDRA query
SOC	system organ class
SPM	second primary malignancy
SQ	subcutaneous
STD	standard deviation
TBILI	total bilirubin
TNF-α	tumour necrosis factor-alpha
TTP	time to progression
TTR	time to objective response
ULN	upper limit of normal
WBC	white blood cell
WHO	World Health Organization

I. Introduction to product submission

Submission details

Type of submission:	New biological entity
Decision:	Approved
Date of decision:	12 September 2016
Date of entry onto ARTG	22 September 2016
Active ingredient:	Elotuzumab
Product name:	Empliciti
Sponsor's name and address:	Bristol-Myers Squibb Australia Pty Ltd Level 2, 4 Nexus Court Mulgrave Vic 3170
Dose form:	Lyophilised powder
Strengths:	300 mg, 400 mg
Container:	Single use vial
Approved therapeutic use:	Empliciti (elotuzumab) is indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.
Route of administration:	IV infusion
Dosage:	· Administration with lenalidomide and dexamethasone: 10 mg/kg administered IV every week (28 day cycle) on Days 1, 8, 15, and 22 for the first two cycles and every 2 weeks thereafter on Days 1 and 15 when administered with lenalidomide and dexamethasone. · Administration with bortezomib and dexamethasone: 10 mg/kg administered IV weekly for the first 2 cycles (21 day cycles) on Days 1, 8, and 15, on Days 1 and 11 for cycles 3 to 8 (21 day cycles), and every 2 weeks on days 1 and 15 for cycles 9 and up (28 day cycles) when administered with bortezomib and dexamethasone.
ARTG numbers:	260052 (300 mg); 260055 (400 mg)

Product background

This AusPAR describes the application by Bristol-Myers Squibb Australia Pty Ltd to register a new biological entity, elotuzumab (Empliciti), for the combination treatment of multiple myeloma in adult patients who have received one or more prior therapies. The drug is a humanised monoclonal antibody (IgG1) against SLAMF7 (Signalling Lymphocyte Activation Molecule Family member 7). The clinical treatment regimen involves IV administration of 10 mg/kg at one- then two-week intervals. SLAMF7 is a cell surface glycoprotein expressed by >95% of multiple myeloma cells, as well as on natural killer (NK) cells and some other lymphocyte populations, and is involved in the regulation of various immune cell functions.

Elotuzumab presents a novel therapeutic option for patients with multiple myeloma. In their study synopses, the sponsor states:

> *Elotuzumab is a humanized immunoglobulin G1 (IgG1) monocolonal antibody (mAb) targeted against Signalling Lymphocyte Activation Molecule Family 7 (SLAMF7, also called CS1), a glycoprotein highly expressed on myeloma cells independent of cytogenetic abnormalities.*
>
> *SLAMF7 is also expressed on natural killer (NK) cells and at significantly lower levels on specific immune cell subsets. SLAMF7 has not been detected on hematopoietic stem cells, nor on other normal solid tissues. Elotuzumab binding to SLAMF7 directly activates NK cells, but not myeloma cells. Elotuzumab bound to myeloma cells via SLAMF7 further activates NK cells via Fc receptors, thereby enabling selective killing of myeloma cells with minimal effects on normal tissue.*

Treatment options for patients with relapse or refractory multiple myeloma (RRMM) have been increased with the availability of thalidomide, lenalidomide and bortezomib pomalidomide based regimens in addition to chemotherapy protocols. Regimens for the treatment of RRMM including thalidomide and its derivatives been incorporated into the most recent clinical practice guidelines of the Myeloma Foundation of Australia (2015); however, these guidelines precede the registration of bortezomib. For patients with RRMM, entry into clinical trials remains a primary management decision, given the ongoing poor outcome for these patients. The use of thalidomide or lenalidomide is limited by the occurrence of peripheral neuropathy and risk of thromboembolism.

Bortezomib, the first registered 26S proteasome inhibitor, is registered for use in patients with newly diagnosed MM eligible for stem cell transplant, in patients ineligible for high dose chemotherapy and for patients with relapsed or refractory disease. Prior to bortezomib registration, the most appropriate therapy for RRMM patients was the combination of lenalidomide and dexamethasone, which had been demonstrated to have increased efficacy over lenalidomide monotherapy.

Regulatory status

At time of submission to TGA, there were no approvals for elotuzumab. The submission was under review in the EU and US.

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Quality findings

Introduction

Structure

Elotuzumab consists of the complementarity determining regions (CDRs) of the mouse antibody, MuLuc63, grafted onto human IgG1 heavy and kappa light chain framework regions.

The predominant molecular isoform, heavy chain without C-terminal lysine and with the G0F/G0F glycoform, has an empirical formula of $C_{6576}H_{10142}N_{1718}O_{2092}S_{42}$ with a calculated molecular mass of 148087 Daltons.

Charge variant forms of the elotuzumab heavy chain exist with and without the C-terminal lysine residue. In heavy chain lacking a C-terminal lysine, glycine is the terminal residue.

Physical and chemical properties

Elotuzumab is a clear to very opalescent, colourless to slightly yellow liquid, pH 6.0, in an aqueous buffer. Based on the amino acid sequence defined by the nucleotide sequence, elotuzumab has an isoelectric point of 7.9 for the predominant charge variant, and a theoretical extinction coefficient of 1.61 mL mg^{-1} cm^{-1}.

Elotuzumab is produced from cell culture using an NS0 mouse myeloma-based cell line. The manufacturing process is initiated by thawing a vial of the working cell bank (WCB). The cell culture is expanded using a series of shake flasks, a cell bag bioreactor, and seed bioreactors to generate a sufficient amount of viable cells to inoculate the production bioreactor.

Elotuzumab is purified using a series of chromatographic and filtration steps. The drug substance in filled bags is frozen and stored at ≤ -35°C.

Stability

Drug substance

The sponsor proposed a shelf life of 36 months at -35°C for the drug substance.

Stability data have been generated under real time and stressed conditions.

Stability data were generated under real time conditions to characterise the stability profile of the substance and to establish a shelf life. The real time data submitted support a shelf life of 36 months when stored at ≤ -35°C.

Drug product

Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product. The product is not photostable.

The proposed shelf life is 36 months when stored at 5°C.

Stability studies have been conducted in accordance with relevant ICH guidelines.

Quality summary and conclusions

There are no objections on quality grounds to the approval of Empliciti (elotuzumab) lyophilised powder for IV infusion vial.

III. Nonclinical findings

Pharmacology

The sponsor has submitted a limited nonclinical package, largely restricted by the species specificity of elotuzumab. This has been partly compensated for by a number of in vitro studies conducted with human cells and tissues, and the phenotypic characterisation of SLAMF7 deficient mice reported in the literature.

Molecular target

SLAMF7 (also called CS1, CD2 subset-1, CD319 and CRACC) is cell surface glycoprotein expressed by >95% of multiple myeloma cells, independent of disease stage or cytogenetic abnormalities.[1] SLAMF7 is also expressed on all NK cells and most CD8+ T cells, and is also detectable on a small proportion of CD4+ T cells and B cells, with little to no expression on granulocytes and haematopoietic stem cells. SLAMF7 is a self-ligand (that is, it is a receptor that recognises as ligand a molecule of itself present on another cell) and is involved in the regulation of various immune cell functions, most particularly the activation of NK cell mediated cytotoxicity. SLAMF7 is recognised to have both stimulatory and inhibitory effects on immune cell function, depending on the presence or absence of co-expression of the intracellular EAT-2 signalling molecule to which it couples. In humans, EAT-2 is highly expressed in NK cells – so that SLAMF7 engagement will have an activating effect – and is also expressed in some CD8+ T cells. EAT-2 does not appear to be expressed in B cells, plasma cells or CD4+ T cells, nor in multiple myeloma cells, so SLAMF7 engagement would be expected to have an inhibitory effect. It should be noted, though, that the role of SLAMF7 in these cell types is not well understood, and stimulation of proliferation (rather than inhibition, and involving cytokine production) has been seen in B cells[2] and there is some evidence that SLAMF7 expression has a tumour promoting effect in multiple myeloma (with SLAMF7 interactions acting to promote cell-cell adhesion, which is known to promote cell growth and survival).[3]

Primary pharmacodynamics

Elotuzumab was shown to bind to human SLAMF7 with high affinity (Kd, 30-45 nM) in surface plasmon resonance assays. Flow cytometry and immunohistochemistry revealed a pattern of binding to human cells and tissues consistent with the known expression pattern of SLAMF7. Elotuzumab bound to 94% of NK cells, 90% of NKT cells, and a significant subset (54%) of CD8+ T cells, and a lower percentage of CD4+ T cells (12%). There was no staining on tissue elements in brain, breast, colon, kidney, liver, oviduct, pancreas, salivary gland, small intestine, spleen, stomach, thymus, thyroid, tonsil, ureter and uterus, except as infiltrating leukocytes in these tissues. Experiments with the murine parent of elotuzumab (MuLuc63; which was demonstrated to have equivalent SLAMF7

[1] Veillette A, Guo H. CS1, a SLAM family receptor involved in immune regulation, is a therapeutic target in multiple myeloma. *Crit. Rev. Oncol. Hematol.* 88: 168-177 (2013).
[2] Lee JK, et al. CS1 (CRACC, CD319) induces proliferation and autocrine cytokine expression on human B lymphocytes. *J Immunol.* 179: 4672-4678 (2007).
[3] Tai YT, et al. Anti-CS1 humanized monoclonal antibody HuLuc63 inhibits myeloma cell adhesion and induces antibody-dependent cellular cytotoxicity in the bone marrow milieu. *Blood* 112: 1329-1337 (2008).

binding affinity and kinetics compared with the humanised antibody) involving a number of additional human tissues also showed no binding other than to infiltrating leukocytes in heart, lung, ovary, prostate, skin, testis and urinary bladder. The murine parent of elotuzumab exhibited strong pericellular staining of the majority (50-95%) of tumour cells in plasmacytoma tissue samples obtained from multiple myeloma patients, consistent with high cell-surface expression of SLAMF7.

Elotuzumab only recognised human SLAMF7. It did not bind to SLAMF7 of any laboratory animal species tested (comprising mouse, rat, rabbit, dog, mini-pig, cynomolgus monkey, rhesus monkey and chimpanzee).

In vitro in functional experiments, elotuzumab induced antibody dependent cell mediated cytotoxicity (ADCC) of a panel of human multiple myeloma cell lines with EC50 values ranging from 9.3-28.7 ng/mL. ADCC of primary tumour cells from multiple myeloma patients (both newly diagnosed and in patients with tumours resistant to bortezomib) by elotuzumab was also demonstrated. Induction of ADCC by elotuzumab was mediated by an interaction between the IgG1 Fc region of the drug and the Fc receptor on NK cells. Elotuzumab had no apparent effect on the health or viability of multiple myeloma cells in the absence of effector cells, and multiple myeloma cells that did not express SLAMF7 were not lysed by elotuzumab. ADCC activity by elotuzumab was significantly enhanced with co-treatment with lenalidomide or pre-treatment with lenalidomide or bortezomib.

In addition to induction of ADCC, elotuzumab was demonstrated to directly activate NK cells in vitro by binding to their SLAMF7, which would serve as a complementary mechanism for anti-tumour activity.

Dose dependent anti-tumour activity was observed with elotuzumab in vivo in SCID mice bearing SLAMF7 expressing human multiple myeloma tumour xenografts. With the OPM2 cell line model, maximum anti-tumour activity (~85% reduction in mean tumour volume and abolition of tumours in 5/9 animals with dosing at 10 mg/kg three times weekly for 2 weeks) was associated with a serum elotuzumab concentration of 70-430 μg/mL; the lowest efficacious dose was associated with serum concentrations of 2-13 μg/mL. These data compare favourably with the serum concentration of elotuzumab achieved with the clinical treatment regimen in patients (minimum, maximum and average steady-state concentrations of 232, 430 and 300 μg/mL determined in the population PK model).

In vivo anti-tumour activity by elotuzumab was found to dependent on Fc/Fc receptor interaction and the presence of NK cells. Consistent with induction of ADCC being the primary mechanism for anti-tumour activity by elotuzumab, loss of in vivo anti-tumour activity was seen with a mutant form of elotuzumab with reduced Fc receptor affinity (3.6 fold lower compared with elotuzumab).[4]

Significantly enhanced anti-tumour activity was seen with elotuzumab in combination with bortezomib, lenalidomide, or pomalidomide (with and without dexamethasone) compared with the various single agents in vivo in mice (OPM2 myeloma xenograft model).

Secondary pharmacodynamics

The specificity of elotuzumab was demonstrated by its recognition of SLAMF7 from humans and not of other species. No secondary pharmacological target was apparent from immunohistochemistry studies using a wide range of human tissues.

[4] Hsi ED, et al. (2008) CS1, a potential new therapeutic antibody target for the treatment of multiple myeloma. *Clin Cancer Res.* 14: 2775-2784 (2008).

Safety pharmacology

No safety pharmacology studies were submitted. This is considered to be acceptable given the nature of the drug and its target – so that effects on cardiovascular, respiratory and central nervous system function are not expected – and given the proposed indication in advanced cancer. In addition, the absence of pharmacodynamic responsiveness to elotuzumab precludes the investigation of toxicity stemming from the drug's primary pharmacological activity in standard laboratory animal species.

Pharmacokinetics

In rhesus monkeys, a single IV dose of elotuzumab yielded roughly dose proportional systemic exposure (serum Cmax and AUC) over the dose range studied (30-100 mg/kg), with no sex difference apparent. As expected for an antibody, clearance was slow (serum half-life, ~8-15 days). Accumulation with repeated dosing was observed in a mouse pharmacology study.

No tissue distribution study was conducted, but the volume of distribution was low in monkeys (~50-60 mL/kg), suggesting that elotuzumab is restricted to the vascular compartment. Metabolism and excretion studies were not conducted, and are not expected for a protein-based drug under the relevant guideline.[5] No nonclinical pharmacokinetic interaction studies were submitted.

Toxicology

General toxicity

The general toxicity of elotuzumab was examined only in a single dose study in rhesus monkeys, which involved IV administration of 30 or 100 mg/kg to one animal/sex/dose group, followed by 44 days observation. The study was not performed according to GLP, but was nevertheless well documented and was conducted in an established laboratory. A comprehensive set of toxicity end points was examined – including, in particular, immunophenotyping and histopathology – with no adverse effects observed up to the highest dose tested. Relative exposure at the NOAEL was ~4 (calculated as the ratio of the animal serum AUC0–∞ [mean of 391 mg·h/mL for the sexes combined] to the serum AUC0–τ in patients at the maximum recommended human dose [100.8 mg·h/mL]). It must be borne in mind, though, that this study is unable to identify toxicity related to the primary pharmacology of the drug (given that elotuzumab does not recognise SLAMF7 in the species) and the capacity to identify any off-target toxicity is limited by the study design (that is, dosing only once and in a small number of animals).

For a biotechnology derived pharmaceutical that is not pharmacologically active in standard laboratory animal species, ICH S6 (R1)[6] encourages toxicity testing using relevant transgenic animals expressing the human receptor or utilising treatment with a homologous protein. A human SLAMF7 transgenic mouse was generated by the sponsor, but was not considered to be a valid alternative model for toxicology testing due to lack of human SLAMF7 expression in both resting and activated T cells in the animals as found in humans. The sponsor has provided no data or commentary regarding the use of an analogous antibody directed toward an animal form of SLAMF7 to investigate the toxicity profile of elotuzumab. This is not considered to be a critical deficiency, though, given the

[5] International Conference on Harmonisation, "Preclinical safety evaluation of biotechnology-derived pharmaceuticals S6(R1)", 12 June 2011.
[6] International Conference on Harmonisation, "Preclinical safety evaluation of biotechnology-derived pharmaceuticals S6(R1)", 12 June 2011.

indication sought and with SLAMF7 knockout mice providing some insight into the likely consequence of pharmacological ablation of SLAMF7 function.

Mice lacking SLAMF7 were reported to appear healthy and showed no evidence of altered NK cell development, but their NK cells killed less efficiently.[7] Expansion of both innate CD8+ T cells in the spleen and NKT cells in the thymus was observed.[8]

The high specificity of elotuzumab and the restricted expression of SLAMF7 across normal cells (i.e., in subsets of leukocytes only and not in tissue parenchyma) suggests that toxicity with elotuzumab is likely to be limited to the haematological and immune systems. The sponsor investigated the potential for such effects in vitro in experiments using human cells. In human whole blood cultures, elotuzumab (≤200 μg/mL; equivalent to approximately half the steady-state serum Cmax in patients) had no effect on total lymphocytes; CD3+, CD4+, CD8+ T cells; and B- and memory B cell counts, while NK cell counts were variably decreased (by 0-45% in samples from 8 donors, with a mean decrease of ~20%; decreases occurred in 5/8 donor samples). In human bone marrow cultures, elotuzumab (≤500 μg/mL; ~1.2-times the clinical serum Cmax) had no significant effect on haematopoietic progenitor proliferation and the formation of erythroid and myeloid colonies.

Genotoxicity and carcinogenicity

No genotoxicity or carcinogenicity studies were submitted, which is acceptable according to ICH S6 (R1) and S9. Elotuzumab is a large protein and is not expected to interact directly with DNA or other chromosomal material.

Reproductive toxicity

No reproductive toxicity studies were submitted. Studies on fertility and pre/postnatal development are not required for pharmaceuticals intended to treat patients with advanced cancer (ICH S6 [R1]), and the absence of an embryofoetal development study is considered to be acceptable given the lack of a pharmacologically relevant laboratory animal species (in accordance with ICH S9).[9]

SLAMF7 does not have a critical role in embryofoetal development, evident by SLAMF7 knockout mice being viable and appearing healthy, and no role in fertility is recognised. As an IgG1 antibody, elotuzumab is expected to cross the placenta, with transfer increasing as pregnancy progresses. Some excretion in milk is also expected, but substantial systemic exposure in an infant with ingestion of maternal milk is not anticipated.

Based on its pharmacology, maternal treatment with elotuzumab may have effects on fetal immune cells (due to exposure to elotuzumab in utero). The drug may also have effects on maintenance of pregnancy, with NK cells seen to play an important role in maternal tolerance of the foetus.[10]

[7] Cruz-Munoz ME, et al. Influence of CRACC, a SLAM family receptor coupled to the adaptor EAT-2, on natural killer cell function. *Nat Immunol.* 10: 297-305 (2009).
[8] De Calisto J, et al. SAP-dependent and -independent regulation of innate T cell development involving SLAMF receptors. *Front Immunol.* 5: 186 (2014).
[9] International Conference on Harmonisation, "Preclinical safety evaluation of biotechnology-derived pharmaceuticals S6(R1)", 12 June 2011.
[10] Sharma S. Natural killer cells and regulatory T cells in early pregnancy loss. *Int. J. Dev. Biol.* 58: 219-229 (2014).

Pregnancy classification

The sponsor has proposed Pregnancy Category C.[11] This is considered to be acceptable given concerns for adverse effects on embryofoetal development with elotuzumab stem from its pharmacological activity, and teratogenic activity is not anticipated.

It is important to note, though, that elotuzumab is to be indicated as combination therapy, and the other anti-cancer agents pose their own risk to the foetus. Of particular note, lenalidomide is contraindicated in pregnancy due to strong concerns for teratogenicity (Category X).[12]

Local tolerance; haemolysis

Elotuzumab was well tolerated locally with IV injection in rabbits and rhesus monkeys. The highest strength tested in animals was close to (5 mg/mL in rabbits) or greater than (10 mg/mL in monkeys) the maximum recommended strength for clinical administration (6.0 mg/mL).

Elotuzumab (≤10 mg/mL) did not induce haemolysis in whole human blood in vitro.

Paediatric use

Elotuzumab is not proposed for paediatric use and no specific studies in juvenile animals were submitted.

Nonclinical summary and conclusions

- In vitro studies established that elotuzumab binds to human SLAMF7 with nanomolar affinity, induces ADCC against SLAMF7 expressing myeloma cells (via an interaction with the Fc receptor of natural killer cells), and is also able to directly activate natural killer cells (by binding to their SLAMF7) to enhance their cytotoxic activity.
- Anti-tumour activity was demonstrated for elotuzumab in vivo in studies conducted in mice bearing human multiple myeloma tumour xenografts. Maximal activity was associated with serum concentrations of elotuzumab of 70-430 μg/mL.
- Pre-treatment or combination treatment with existing anti-cancer agents (lenalidomide, pomalidomide, bortezomib) significantly enhanced elotuzumab's induction of ADCC (in vitro) and anti-tumour activity (in vivo), supporting the proposed combination use of the product.
- Elotuzumab only recognised human SLAMF7, and not SLAMF7 from any laboratory animal species tested (mouse, rat, rabbit, dog, mini-pig, cynomolgus monkey, rhesus monkey and chimpanzee). A valid transgenic mouse model is not available. The absence of a pharmacologically relevant animal species has restricted the sponsor's ability to characterise the toxicity profile of elotuzumab. This has been partly compensated for by other nonclinical data (in vitro studies with human cells and tissues; phenotypic characterisation of SLAMF7 deficient mice).
- No adverse effects were observed in rhesus monkeys administered elotuzumab at ≤100 mg/kg IV. This study provides only very limited support for safety, though.
- Elotuzumab was well tolerated locally with IV injection in rabbits and monkeys.

[11] Category C: Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.
[12] Category X: Drugs which have such a high risk of causing permanent damage to the foetus that they should not be used in pregnancy or when there is a possibility of pregnancy.

- Immunohistochemistry studies examining the cross reactivity of elotuzumab identified no secondary pharmacological target for the drug. The high specificity of the antibody and the pattern of expression of SLAMF7 (noting that is it not expressed in tissue parenchyma) suggests that toxicity with elotuzumab will be limited to the haematological and immune systems.
- Consistent with relevant ICH guidelines,[13] no genotoxicity, carcinogenicity or reproductive/development toxicity studies were conducted with elotuzumab. SLAMF7 is not seen to have a critical role in embryofoetal development, based on the viability and normal appearance of SLAMF7 knockout mice. Considering the drug's pharmacology, use in pregnancy may have effects on fetal immune cells and modify maternal tolerance to the foetus (due to the involvement of natural killer cells). Placement in Pregnancy Category C,[14] as the sponsor proposes, is supported.
- While limited, the nonclinical program for elotuzumab is considered to be adequate, and there are no nonclinical objections to the registration of Empliciti for the proposed indication. The safety assessment will chiefly rely on clinical data.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

Multiple myeloma is a malignant disease of plasma cells, and currently has a median overall survival of approximately 5 years. Despite improvements in treatment outcomes with proteasome inhibitors and immunomodulatory drugs, most patients will relapse, and new treatment approaches are needed. Combination therapy may overcome drug resistance and improve long-term treatment outcomes. Lenalidomide, an immunomodulatory drug, in combination with dexamethasone; and bortezomib, a proteasome inhibitor, in combination with dexamethasone, are standard regimens in patients with relapsed or refractory disease. Three drug combinations (immunomodulatory agent, proteasome inhibitor and dexamethasone) are emerging for patients with previously treated multiple myeloma but may be limited by toxic effects. Consequently, agents with new mechanisms of action that can be combined with existing therapies without an increase in serious toxicity are needed.

Elotuzumab is a first-in-class humanised immunoglobulin G1 immunostimulatory monoclonal antibody targeted against SLAMF7, a glycoprotein expressed on myeloma and natural killer cells but not on normal tissues that enables selective killing of myeloma cells with minimal effects on healthy tissue. Over 95% of bone marrow myeloma cells express SLAMF7 independently of cytogenetic abnormalities. Elotuzumab exerts a dual effect by directly activating natural killer cells and mediating ADCC. SLAMF7 mediates activating signals in NK cells by coupling with its adapter protein EAT-2. In myeloma cells, SLAMF7 signalling is compromised owing in part to lack of EAT-2 expression and therefore, elotuzumab does not induce proliferation of myeloma cells.

[13] International Conference on Harmonisation, "Preclinical safety evaluation of biotechnology-derived pharmaceuticals S6(R1)", 12 June 2011.
[14] Category C: Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

Contents of the clinical dossier

The clinical dossier documented a full clinical development program of pharmacology, efficacy and safety.

The submission contained the following clinical information:

- One Phase III clinical efficacy/safety study in adults of elotuzumab in combination with lenalidomide and dexamethasone versus lenalidomide and dexamethasone (Study CA204004) in which pharmacokinetic and pharmacodynamic properties of elotuzumab were also assessed.
- One Phase II clinical efficacy/safety study in adults of elotuzumab in combination with bortezomib and dexamethasone versus bortezomib and dexamethasone (Study CA204009) in which pharmacokinetic and pharmacodynamic properties of elotuzumab were also assessed.
- Two Phase I efficacy/safety studies (Studies HuLuc63-1702 and HuLuc63-1703), which also provided pharmacodynamic and pharmacokinetic data.
- One Phase IIa efficacy/safety study of elotuzumab combined with thalidomide and dexamethasone (Study CA204010), which also provided pharmacodynamic and pharmacokinetic data.
- Three Phase I safety/PK studies (Studies CA204007, CA204005, and HuLuc63-1701)
- One Phase II efficacy/safety/PK biomarker study (Study CA204011)

Good clinical practice

All of the studies at US sites were conducted under a United States Investigational New Drug Application (IND). All non-US sites complied with local regulations. All of the sites (US and non-US) were conducted in accordance with recognised international scientific and ethical standards, including but not limited to the International Conference on Harmonisation guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki. These standards are consistent with the requirements of the US Code of Federal Regulations (CFR) Title 21, Part 312 (21CFR312), and the European Community Directive 2001/20/EC.

The protocol, consent form, study subject information sheets, and advertisement were submitted by each investigator to a duly constituted Institutional Review Board for review and approval before study initiation. All patients provided written informed consent after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures.

Pharmacokinetics

Studies providing pharmacokinetic data

The PK of elotuzumab was studied in 619 patients with MM who received doses of 0.5 (N = 3), 1.0 (N = 4), 2.5 (N = 9), 5.0 (N = 10), 10 (N = 483), or 20 (N = 110) mg/kg IV either as monotherapy, in combination with lenalidomide/dexamethasone, in combination with bortezomib (and dexamethasone if added at the end of Cycle 2 or 3), or in combination with bortezomib/dexamethasone.

It should be noted that Abbott Biotherapeutics validated an in-house ELISA method to quantitate elotuzumab from patient samples in support of Phase I and II clinical trials. Because the initial Phase I study was a dose escalation study, an assay with a low sensitivity was desired. The resulting assay had a minimum required dilution (MRD) of

1:10 for serum samples and incorporated background subtraction whereby the signal obtained with a patient's baseline sample was subtracted from the same patient's post-dose sample signals prior to determining the elotuzumab concentration in the post-dose samples. Elotuzumab is being jointly developed by AbbVie Biotherapeutics (ABR) and BMS, with BMS having primary responsibility for running Phase III studies. For PK assay support, the ELISA was transferred to Tandem Labs and the assay was updated to have a higher MRD and remove the background subtraction since it was not necessary to have very low assay sensitivity for Phase III. Thus, an ELISA was validated at Tandem using a 1:200 MRD. Since the PK data obtained from Abbott for Phase I/II will be used for regulatory filing(s), and the Phase III study has a sparse PK sampling design, it was determined that a cross validation of the assay was necessary to assess comparability of the two methods. However, the AbbVie PK assay SOP 30-0592_00 and the BMS PK assay TLIAM-0180 did not meet the pre-established cross-validation criteria. This prompted a sensitivity analysis using a PPK approach which demonstrated that inclusion of PK data from 2 of the AbbVie studies (HuLuc63-1701 and HuLuc63-1703) had minimal impact on the PPK model parameters of elotuzumab. Nevertheless, only PK data from BMS clinical studies (CA204004, CA204005, CA204007, and CA204011) were used for PPK analysis and results from this analysis were used to provide PK information to the labelling.

Single dose PK of elotuzumab was investigated in 4 studies (HuLuc63-1701, HuLuc63-1702, CA204005, and CA204007), after the administration of the first IV dose. The PPK analyses for elotuzumab / lenalidomide / dexamethasone were based on data from a Phase I study (CA204005), a Phase Ib study (CA204007), a Phase II study (CA204011), and a Phase III study (CA204004). Data from these studies comprised the PPK analysis dataset (375 subjects; 6958 samples). The PPK model for elotuzumab / lenalidomide / dexamethasone that was developed with data from the above 4 studies was evaluated and refined with additional PK data from the randomised Phase II Study CA204009 (74 subjects; 476 samples).

Evaluator's conclusions on pharmacokinetics

The application included detailed characterisations of the clinical pharmacology of elotuzumab, which were based on preclinical studies and clinical development in Phase I, II and III studies. Pharmacokinetic assessments included single and multiple dose PK, dose proportionality, accumulation ratio, and impact of renal dysfunction.

Pharmacokinetic assessments were performed for elotuzumab monotherapy in a Phase 1 study (HuLuc63-1701) and a Phase II study (CA204011); in combination with bortezomib and dexamethasone in a Phase I study (HuLuc63-1702), and a Phase II study (CA204009); in combination with lenalidomide and low-dose dexamethasone in a Phase I study (CA204005), a Phase Ib study (CA204007), a Phase Ib/II study (HuLuc63-1703), and a Phase III study (CA204004).

Single dose PK of elotuzumab was investigated in 4 studies (HuLuc63-1701, HuLuc63-1702, CA204005, and CA204007), after the administration of the first IV dose.

The PPK analyses for elotuzumab / lenalidomide / dexamethasone were based on data from a Phase I study (CA204005), a Phase Ib study (CA204007), a Phase II study (CA204011), and a Phase III study (CA204004). Data from these studies comprised the PPK analysis dataset (375 subjects; 6958 samples). The PPK model for elotuzumab / lenalidomide / dexamethasone that was developed with data from the above 4 studies was evaluated and refined with additional PK data from the randomised Phase II Study CA204009 (74 subjects; 476 samples).

All studies were conducted as planned and protocol deviations and violations were provided. Collection and storage of samples were described and adequate. The assays used to determine plasma concentrations were adequately described and validated. In support

of Phase I and II clinical trials, an Abbott Biotherapeutics in-house ELISA method with a low sensitivity was used. For PK assay support in Phase 3 studies, the ELISA was transferred to Tandem Labs and the assay was updated to have a higher MRD and remove the background subtraction, since it was not necessary to have very low assay sensitivity. A cross validation of the assays was performed to compare the two methods. However, the AbbVie PK assay SOP 30-0592_00 and the BMS PK assay TLIAM-0180 did not meet the pre-established cross-validation criteria. A sensitivity analysis using a PPK approach demonstrated that inclusion of PK data from 2 of the AbbVie studies (HuLuc63-1701 and HuLuc63-1703) had minimal impact on the PPK model parameters of elotuzumab. However, only PK data from BMS clinical studies (CA204004, CA204005, CA204007, and CA204011) were used for PPK analysis and results from this analysis were used to provide PK information for the labelling.

The PK of elotuzumab in MM patients was nonlinear. Following administration of a single dose, elotuzumab clearance decreased from 17.5 to 5.8 mL/day/kg, and the area under the serum concentration time curve increased in a greater than dose proportional manner over the dose range of 0.5 to 20 mg/kg. The nonlinearity of elotuzumab PK was consistent with target mediated drug disposition and was described by a two compartment model with zero order IV infusion, parallel linear and Michaelis-Menten elimination from the central compartment and time dependent, target mediated elimination from the peripheral compartment.

For all provided studies inclusion/exclusion criteria were appropriate and compliance with treatment was acceptable.

Population PK based simulations indicated that following administration of elotuzumab at 10 mg/kg in combination with lenalidomide/dexamethasone or bortezomib/dexamethasone, values for the mean effective half-life of elotuzumab were 33.5 and 43.1 days, respectively, and an AUC accumulation ratio of 7.42 and 9.41, respectively. The prolonged half-lives were in part attributable to concomitant dexamethasone administration. After discontinuation of treatment, serum elotuzumab concentrations decreased to approximately 3% (approximately 97% washout) of the population predicted steady-state maximal concentration by 3 months. Nonspecific (linear) clearance of elotuzumab increased with increasing body weight and the nonlinear clearance increased with baseline M-protein.

Renal function did not significantly affect elotuzumab PK, indicating that no dose adjustment is required in patients with renal dysfunction, which includes ESRD undergoing dialysis. No clinically important differences in the clearance of elotuzumab were found between patients with mild hepatic impairment and patients with normal hepatic function. Population PK analysis suggested no differences in clearance of elotuzumab based on age, sex, race, baseline LDH, albumin, β2-microglobulin, mild hepatic function, renal function, and ECOG performance status.

Monoclonal antibodies are not direct inhibitors/inducers of metabolising enzymes and are eliminated by metabolic pathways that are divergent from small molecules; consequently direct drug-drug interactions (DDIs) between mAb and small molecules are thought to be unlikely. This was considered an acceptable explanation for not performing formal PK DDI studies. Elotuzumab treatment resulted in transient changes in circulating cytokines across the dose range 0.1 to 20 mg/kg that were not time or dose dependent and, therefore, are not considered to be clinically meaningful. This finding suggested elotuzumab has a low potential for modulating CYP enzymes and is a low risk to impact the PK of other drugs and for therapeutic protein-drug interactions.

The 10 mg/kg dose of intravenous elotuzumab on Days 1, 8, 15, and 22 during the first two cycles and then on Days 1 and 15 starting with the third cycle, given in 28 day cycles until disease progression, in combination with lenalidomide/dexamethasone or in

combination with bortezomib/dexamethasone provided steady state target exposure in the proximity of 70 µg/mL or greater, the target threshold concentration associated with maximal efficacy observed in the preclinical xenograft multiple myeloma mouse model.

The proposed PI is an adequate summary of the PK presented in the submission.

Pharmacodynamics

Studies providing pharmacodynamic data

Patient PD and PK/PD data were included in the following study reports: HuLuc63-1701, HuLuc63-1702, CA204011, and CA204009.[15]

Evaluator's conclusions on pharmacodynamics

Serum concentrations of elotuzumab between 10 and 100 µg/mL resulted in > 80% saturation of SLAMF7 receptors on antigen rich peripheral blood NK cells, bone marrow NK cells, and bone marrow plasma cells. Elotuzumab concentrations greater than 10 µg/mL are achieved at pre-dose on Day 8 following the first infusion; and higher concentrations are sustained after multiple dosing with the recommended 10 mg/kg dosage of elotuzumab to relapsed/refractory MM patients. At these concentrations, in vitro data suggested near complete saturation of SLAMF7 receptors by elotuzumab. The target threshold concentration of elotuzumab associated with maximal efficacy in the preclinical xenograft mouse model was identified as 70 µg/mL, with an upper limit of 430 µg/mL. These data indicated that administration of the recommended 10 mg/kg elotuzumab dose resulted in serum concentrations that were at or higher than those expected to result in anti-tumour activity in a clinical setting.

Transient decreases in all lymphocytes, including NK cells, were observed post dose with the first infusion of elotuzumab which was attenuated after repeated administration. This transient decrease occurred in all lymphocyte subsets examined regardless of their SLAMF7 expression. Lymphocyte cell trafficking out of the periphery may be one possible explanation to account for the reduction in cell counts due to the transient increase in interferon gamma-induced protein 10 (IP-10), a chemokine that stimulates migration of activated T cells and NK cells.

Elotuzumab has the propensity to cause the release of cytokines, chemokines, and growth factor in vitro as well as in vivo. A transient increase in three chemokines or cytokines was observed: tumour necrosis factor α (TNF-α), IP-10, and monocyte chemoattractant protein 1 (MCP-1), with a trend for levels to return to baseline. Other chemokines or cytokines, including IL-6, showed a similar pattern. Reactions due to cytokine release were minimized by hydration and diuresis, premedications, and incremental increases in the rate of infusion of elotuzumab. There was no relationship between SLAMF7 expression on plasma cells in bone marrow aspirates at baseline and best confirmed clinical response as determined by International Myeloma Working Group (IMWG) criteria or PFS in subjects treated with elotuzumab in combination with lenalidomide/dexamethasone.

[15] See Attachment 2 for further details.

Dosage selection for the pivotal studies

Pivotal study CA204004

Based on the assessments of clinical PK, PD, efficacy, and safety, the elotuzumab was administered weekly at a dose of 10 mg/kg IV (Days 1, 8, 15, and 22, -1 to + 3 days) for the first 2 cycles and every 2 weeks (Day 1 and 15) thereafter. Dose reductions were not permitted and doses that fell outside of the pre-specified window for Cycles 1 and 2 were to be skipped. In Cycle 3 and beyond, elotuzumab dosing could be delayed by up to 1 week as clinically indicated. If the dose was not able to be administered within 1 week, then the dose was to be skipped and the remaining doses of elotuzumab were to continue according the protocol defined schedule. The 10 mg/kg dose of elotuzumab was chosen since it was the dose selected for Phase III MM studies in the clinical development program. This dose showed similar safety, efficacy, and toxicity as the highest elotuzumab dose tested in clinical studies (20 mg/kg), and was sufficient to saturate the CS1 target on MM cells in bone marrow. Further, the trough PK levels at 10 mg/kg were above those needed for activity against myeloma in preclinical models.

Efficacy

Studies providing efficacy data

Studies for elotuzumab as combination therapy for the treatment of multiple myeloma in adult patients who have received one or more prior therapies:

- Study CA204004: A Phase III, randomized, open label trial of lenalidomide/dexamethasone with or without elotuzumab in relapsed or refractory multiple myeloma
- Study CA204009: A Phase II, randomised study of bortezomib/dexamethasone with or without elotuzumab in subjects with relapsed/refractory multiple myeloma
- Study HuLuc63-1702: A Phase I/II, multicentre, open label, dose escalation study of elotuzumab and bortezomib in subjects with multiple myeloma following one to three prior therapies
- Study HuLuc63-1703: A Phase Ib/II, multicentre, open label, dose escalation study of elotuzumab in combination with lenalidomide and dexamethasone in subjects with relapsed multiple myeloma
- Study CA204010: A Phase IIa single arm study of elotuzumab in combination with thalidomide and dexamethasone in subjects with relapsed and/or refractory multiple myeloma

Evaluator's conclusions on efficacy

For the treatment of relapsed/refractory multiple myeloma with elotuzumab in combination with lenalidomide/dexamethasone, the sponsors have provided one pivotal Phase III study (CA204004), supported by one Phase II study (HuLuc63-1703).

Study CA204004 was a randomised, open label, multicentre Phase III trial, which evaluated the efficacy and safety of elotuzumab in combination with lenalidomide and dexamethasone, as compared with lenalidomide and dexamethasone alone, in patients with relapsed or refractory multiple myeloma. Eligible patients were randomly assigned in a 1:1 ratio and stratified according to the baseline β2-microglobulin level (<3.5 mg per litre versus ≥3.5 mg per litre), the number of previous therapies (one versus two or three), and previous immunomodulatory drug therapy (none versus thalidomide only or other).

The co-primary end points were progression free survival and the overall response rate (partial response or better). Efficacy endpoints were centrally assessed on the basis of standard criteria of the European Group for Blood and Marrow Transplantation and International Myeloma Working Group.

At 1 year, the rate of PFS in the elotuzumab group was 68% (95% confidence interval [CI], 63 to 73) versus 57% (95% CI, 51 to 62) in the control group; the 2-year rates were 41% (95% CI, 35 to 47) and 27% (95% CI, 22 to 33), respectively. Median PFS in the elotuzumab group was 19.4 months (95% CI, 16.6 to 22.2) versus 14.9 months (95% CI, 12.1 to 17.2) in the control group, for a hazard ratio of 0.70 (95% CI, 0.57 to 0.85; P<0.001), indicating a relative reduction of 30% in the risk of disease progression or death. In relapsed/refractory multiple myeloma, these data show that the combination of elotuzumab with lenalidomide and dexamethasone provide clinically meaningful and statistically significant improvements in treatment outcomes. Specifically, Kaplan-Meier curves for progression free survival showed early and increasing separation between the two groups over time. The benefit with respect to progression-free survival was further confirmed by means of multiple sensitivity analyses. Follow-up for survival outcomes is ongoing.

The external validity of this study was high and the results are generalizable to relapsed/refractory multiple myeloma patients that would be encountered in typical clinical haematology settings. The benefit of adding elotuzumab to lenalidomide and dexamethasone was observed across most pre-specified subgroups, including patients resistant to the most recent line of therapy, those with previous exposure to immunomodulatory drugs or bortezomib, and patients 65 years of age or older. Furthermore, this study had a high proportion of patients (30%) with a high-risk cytogenetic profile, when defined as positive results on testing for t(4;14) or t(14;16) or >/= 60% cells with del(17p).

There was an absolute difference of 13 percentage points in the overall response rate in favour of the elotuzumab group. It was noted that there were a lower number of complete responses in the elotuzumab group compared to the control group. However, it is possible that the measurement of the M-protein was affected by the presence of therapeutic antibody on serum EPG and IFE, which has been observed in trials of other mAbs, and that the number of CRs was under estimated.[16]

In Study HuLuc63-1703, a single group, Phase Ib/II trial of elotuzumab in combination with lenalidomide and dexamethasone, the primary efficacy endpoint for the Phase II portion of the study was the objective response according to the IMWG. The analysis population was the ITT population. Sixty-one of the 73 subjects (83.6%) had an objective response (95% CI: 73.0-91.2%), consistent with the objective response rate in the Phase 1b portion of the trial.

In the Phase II portion of HuLuc63-1703, PFS in the elotuzumab plus lenalidomide and dexamethasone group was 28.62 months (95% CI: 16.6-43.1) overall, which was longer than 21 months for investigator determined PFS in CA204004. However, patients in HuLuc63-1703 were younger (median age, 63 years) and fewer had a high-risk cytogenetic profile, whereas there were more patients with co-existing illnesses in CA204004.

[16] 1Genzen JR, et al. Detection of a monoclonal antibody therapy (ofatumumab) by serum protein and immunofixation electrophoresis. *Br J Haematol.* 155: 123-5 (2011); McCudden CR, et al. Interference of monoclonal antibody therapies with serum protein electrophoresis tests. *Clin Chem.* 56: 1897-9 (2010); Axel AE, et al. Development of clinical assay to mitigate daratumumab, an IgG1K monoclonal antibody, interference with serum immunofixation (IFE) and clinical assessment of M-protein response in multiple myeloma. *Cancer Res.* 74: 2563. Abstract (2014).

For the treatment of relapsed/refractory multiple myeloma with elotuzumab in combination with bortezomib/dexamethasone, the sponsors have provided one Phase II, multicentre, open label, randomized study (CA204009), and one Phase I/II, multicentre, open label, dose escalation study (HuLuc63-1702), although the Phase II part of this trial was not conducted. The Phase II study design of CA204009 presents moderate quality evidence of efficacy, which would have been better provided by a Phase III study, however protection from bias in selecting patients has to some extent been provided by the inclusion of multiple study sites.

Study CA204009 randomised subjects in a 1:1 ratio to receive either elotuzumab in combination with bortezomib and dexamethasone or bortezomib and dexamethasone alone, and were stratified based on prior proteasome inhibitor use, presence of at least one FcγRIIIa V allele, and number of prior lines of therapy. The primary endpoint was PFS, and for analysis, required at least 103 progression events. This number of events was to ensure that a one-sided, 0.15 (equivalent to a two-sided 0.30) significance level log-rank test would have 80% power if the median PFS times in the control and investigational arms were 10 months and 14.5 months, respectively, that is, if the hazard ratio of the investigational arm to the control arm was 0.69. The treatment group comparison at the final analysis was based on a two-sided 0.3 alpha level.

As of the database lock, 41 subjects did not have a progression event; 25 subjects (32.5%) in the E-Bd arm and 16 subjects (21.3%) in the Bd arm. A total of 52 subjects (67.5%) in the EBd arm and 59 subjects (78.7%) in the Bd arm had a progression event. The median follow-up time was 15.93 months for the E-Bd group and 11.70 months for the Bd group. The trial met the primary endpoint of PFS with a hazard ratio of 0.72 (70% CI: 0.59, 0.88; p-value = 0.0923). The median PFS for subjects treated with E-Bd was 9.72 months (95% CI: 7.43, 12.16) compared to 6.90 months (95% CI: 5.09, 10.15) for subjects treated with Bd.

HuLuc63-1702 was a Phase I/II dose escalation study of elotuzumab and bortezomib in subjects with multiple myeloma following one to three prior therapies, however the Phase II stage was not performed and efficacy was a secondary objective of the Phase I stage. Subjects who completed at least 2 cycles of treatment, or progressed before completing 2 cycles of treatment, were to be considered as efficacy evaluable. Fourteen of 27 subjects (51.9%) in the Efficacy Evaluable population had disease progression while receiving study treatment. The median time to disease progression overall was 9.5 months.

In efficacy and safety studies, the sponsors included Study CA204010, which was a Phase IIa single arm study of elotuzumab in combination with thalidomide and dexamethasone in subjects with relapsed and/or refractory multiple myeloma. Clinical activity was an exploratory objective in this study, the primary aim of which was to determine safety and tolerability. Objective response in this study was 40% (16 of 40 treated subjects, 95% CI: 24.9, 56.7) and the median PFS was 3.9 months.

The Phase III and Phase II efficacy studies provided by the sponsor show that elotuzumab can be successfully combined with lenalidomide, and have demonstrated synergy in relapsed/refractory multiple myeloma patients, with enhanced response rate and improvemed in PFS compared to a combination of lenalidomide and dexamethasone. The results for a Phase II study of the combination of elotuzumab, bortezomib and dexamethasone are promising and demonstrate clinical efficacy, however further validation in a Phase III study in a larger patient population is warranted. Similarly, validation of efficacy is required for the combination of elotuzumab, thalidomide and dexamethasone.

Safety

Studies providing safety data

Across three separate Phase I trials, dose escalation up to 20 mg/kg (range: 5-20 mg/kg) was achieved without reaching a maximum tolerated dose. The safety population is summarised in Table 1.

Table 1: Overview of Subjects Treated with Elotuzumab in Completed and Ongoing Studies

Population	Elotuzumab Dose (mg/kg)	Enrolled / Randomized N	Elotuzumab treated N	Safety Data Provided for Submission
Elotuzumab in Combination with Lenalidomide/Dexamethasone				
CA204004, RR MM	10	646	318	Pooled E-Ld population; Completed CSR
HuLuc63-1703, RR MM	5, 10, 20	102	101	
CA204005, RR MM	10, 20	7	6	
CA204007, RI MM	10	35	26	
Elotuzumab in Combination with Bortezomib/Dexamethasone				
CA204009, RR MM	10	152	75	Completed CSR
HuLuc63-1702, RR MM	2.5, 5, 10, 20	28	28	Completed CSR
Other Studies - Elotuzumab Monotherapy				
CA204011, SM	10, 20	41	31	Completed CSR
HuLuc63-1701, RR MM	0.5, 1.0, 2.5, 5.0, 10, or 20	35	34	Completed CSR
Ongoing E-Ld Studies				
CA204006, ND MM	10	~750[b]	~371[c]	Select AE summaries
CA204112,	10	~84[b]	69[c]	Select AE

Population	Elotuzumab Dose (mg/kg)	Enrolled / Randomized N	Elotuzumab treated N	Safety Data Provided for Submission
RR MM/ ND MM				summaries

a. N's reflect number randomized for CA204004, CA204009 and number enrolled for all other studies. b. N reflects approximate number to be randomized (for CA204006) or enrolled (for CA204112). c. For ongoing study CA204112, number treated as of 15-May-2015. For CA204006, number of elotuzumab treated is approximate based on 742 treated subjects as of 14 Nov 2014.
IMiD = immunomodulatory drug; MM = multiple myeloma; ND = newly diagnosed; PI = proteasome inhibitor; RI = renally impaired; RR = Relapsed/Refractory; SM = smoldering myeloma

Pivotal efficacy study

In the pivotal study, safety was an exploratory endpoint. The safety assessments included the following and were reported for drug related AEs and regardless of causality:

- Frequency of on-study AEs and on-study serious AEs [SAE]
- Frequency of on-study AEs and on-study SAEs leading to discontinuation
- Frequency of AEs of special interest
- Frequency of deaths
- Laboratory assessments for safety, including hematology, liver parameters, renal/electrolyte parameters
- Electrocardiograms (ECG)
- Vital signs and physical measurements

Adverse Events of Special Interest

Infusion Reactions

Infusion reaction is a known elotuzumab toxicity and was defined as any investigator-reported non-serious or serious IRs on the day of or the day after elotuzumab infusion.

Secondary Malignancies

Secondary malignancies were assessed continuously on-treatment and during follow-up.

Adverse Events of Infection

Adverse events of infection were characterised in detail since elotuzumab may affect some cellular components of the immune system. To further identify the types and severity of infections, summaries of all relevant AEs, AEs leading to discontinuation, SAEs (any grade, Grade 3-4), and deaths within 60 days of the last dose were analyzed for all PTs under the SOC of "infections and infestations". Additional analyses were also included in order to:

- characterize the time and duration of infections
- determine the frequency of opportunistic infections
- determine the frequency of infections by prior stem cell transplant
- summarize the worst CTC grade for ALCs by prior stem cell transplant

ECG Variables

Electrocardiogram assessment for subjects treated with elotuzumab was added through amendments at selected sites. Electrocardiograms were collected in triplicate and

assessed at 13 time points over the course of Cycles 1 through 3 by an independent ECG core laboratory (Biomedical Systems, St. Louis, Missouri) blinded to treatment, subject and study day. The time points covered baseline, maximum concentration, and periodic on-therapy assessments.

Studies that assessed safety as a primary outcome

Studies that assessed safety as a primary outcome were studies CA204005, CA204010, and HuLuc63-1701. PK studies in renal failure were included in Study CA204007 and ECG changes were a primary outcome in the biomarker study, HuLuc63-1701.

Study CA204005

- Phase I: Multiple Ascending Dose Study of Elotuzumab (BMS-901608) in combination with Lenalidomide/Low-Dose Dexamethasone in Patients with Relapsed or Refractory Multiple Myeloma in Japan

The primary objective was to assess the safety and tolerability of elotuzumab when given in combination with lenalidomide and low-dose dexamethasone (E-Ld) in subjects with relapsed or refractory multiple myeloma (MM) in Japan.

Secondary objectives were:

- To assess the clinical activity of E-Ld, according to the European Group for Blood and Marrow Transplantation(EBMT) criteria
- To assess the pharmacokinetics (PK) of elotuzumab when administered in combination with lenalidomide/dexamethasone.
- To evaluate the immunogenicity of elotuzumab.

Safety analyses were conducted using the all-treated subject population. Worst toxicity grades per subject were tabulated for AEs and laboratory measurements. All recorded AEs, SAEs, and AEs leading to study therapy discontinuation were listed and tabulated by system organ class, and preferred term. Vital signs and clinical laboratory test results were listed and summarized.

Seven subjects were enrolled and 6 were treated with elotuzumab (N = 3 subjects receiving 10 mg/kg E-Ld and N = 3 subjects receiving 20 mg/kg E-Ld). One subject was not treated due to no longer meeting study criteria. Three subjects are currently enrolled in the follow-up period.

Study CA204010

- Phase IIa single-arm study of elotuzumab in combination with thalidomide and dexamethasone in relapsed and/or refractory multiple myeloma

Primary Objective: To determine the safety and tolerability of elotuzumab in combination with thalidomide and dexamethasone in subjects with relapsed and/or refractory multiple myeloma) as assessed by the incidence of severe (Grade 3 or higher) non-hematologic adverse events (AEs).

Secondary Objectives: To determine the frequency of dose modifications due to AEs in subjects with relapsed/refractory MM treated with E-Td.

Exploratory Objectives:

- To evaluate the general safety of the E-Td regimen
- To evaluate the clinical activity of E-Td as defined by the modified International Myeloma Working Group (IMWG) response criteria

- To assess safety and clinical activity of thalidomide, dexamethasone, elotuzumab, and cyclophosphamide in those subjects who have a suboptimal response to E-Td

Study CA204007

- A Phase Ib study of elotuzumab in combination with lenalidomide and dexamethasone in subjects with multiple myeloma and normal renal function, severe renal impairment, or end stage renal disease requiring dialysis.

Primary Objective:

- To assess the effect of severe renal impairment (SRI) and end stage renal disease (ESRD) on the single-dose pharmacokinetics (PK) of elotuzumab.

Secondary Objectives:

- To evaluate the safety of elotuzumab in combination with orally administered lenalidomide and low dose dexamethasone (E-Ld) in multiple myeloma (MM) subjects with and without SRI and ESRD.
- To evaluate the immunogenicity of elotuzumab in subjects with and without SRI and ESRD.

Exploratory Objectives:

- To assess the degree and rapidity of renal function improvement with E-Ld in subjects with SRI and ESRD.
- To assess anti-myeloma activity of E-Ld in MM subjects with SRI and ESRD.
- To assess PK results in relation to estimated glomerular filtration rate (eGFR) as determined by the Modification of Diet in Renal Disease (MDRD) formula.

Study HuLuc63-1701

- Phase I, Multi Centre, Open Label, Dose Escalation Study of Elotuzumab (Humanized anti-CS1 Monoclonal IgG1 antibody) in Subjects with Advanced Multiple Myeloma

Primary objectives:

- To identify the maximum tolerated dose (MTD) of elotuzumab administered intravenously
- To evaluate the safety of elotuzumab intravenously given every other week

Secondary objectives:

- To evaluate the PK of elotuzumab
- To evaluate the immunogenicity of elotuzumab
- To evaluate the potential clinical activity of elotuzumab in relapsed/refractory MM, as defined by the European Group for Blood and Marrow Transplantation (EBMT) response criteria.
- To evaluate the long-term safety of elotuzumab given intravenously every other week
- To evaluate the PD of elotuzumab

Patient exposure

The clinical development program for elotuzumab included data in subjects with MM from Phase I, II, and III studies. Subjects received the proposed dose of 10 mg/kg elotuzumab in the E-Ld, E-Bd, and E-Td regimens and as elotuzumab monotherapy. Dose ranging Phase I/II studies, with monotherapy or in combination with Ld or Bd, identified 10 mg/kg as a

potential efficacious dose for elotuzumab. The recommended elotuzumab dosage was selected based upon an integrated assessment of data from in vitro, preclinical, and clinical studies.

The majority of the safety results are derived from the 10 mg/kg elotuzumab dose, based on the percentage of subjects treated at that dose.

This submission includes safety data from the following clinical studies:

- E-Ld Regimen
  - CA204004 (ELOQUENT-2)
  - HuLuc63-1703
  - CA204005.
  - CA204007
- E-Bd Regimen
  - CA204009
  - HuLuc63-1702
- Other Supportive Completed Studies
  - CA204010
  - 2 elotuzumab monotherapy studies
    - § HuLuc63-1701
    - § CA204011

Overall, the E-Ld and E-Bd regimens with 10 mg/kg of elotuzumab were well tolerated, based on a high percentage of subjects able to tolerate ≥ 90% of the planned doses (81.6% and 73.3%, respectively).

Evaluator's conclusions on safety

The biological expression of SLAMF7 on malignant plasma cells and NK cells, minimal expression in a subset of normal immune cells, and absent expression on normal tissue and haematopoietic stem gives elotuzumab a favourable safety profile. Elotuzumab, in combination with lenalidomide, thalidomide or bortezomib was well tolerated in relapsed/refractory MM patients with 1 or more prior therapies, and with the exception of infusion reactions the safety profile of the elotuzumab combination therapy was similar to that of lenalidomide, thalidomide or bortezomib alone. The size of the safety database was considered adequate to define the safety profile of elotuzumab at the intended registrational dose.

In combination with lenalidomide, lymphopenia was observed in elotuzumab-treated patients, which may reflect alterations in lymphocyte trafficking. However, there was no evidence of increased autoimmunity. The rate of herpes zoster infection was greater in the elotuzumab group than in the control group (incidence per 100 patient-years, 4.1 versus 2.2); 1 patient in the control group discontinued treatment because of herpes zoster infection. Other than herpes zoster, there was no increase in the incidence of opportunistic infections. In Study CA204004, a similar proportion of patients in each study group (2%) died from an adverse event. In the elotuzumab group, 2 patients died from infections and 1 each from pulmonary embolism, gastrointestinal cancer, and the myelodysplastic syndrome. In the control group, 5 patients died from infections and 1 from pulmonary embolism.

Infusion reactions are an AE of special interest that was identified in all elotuzumab clinical studies. When the recommended guidelines for premedication were followed, infusion reactions were uncommon and were generally mild to moderate in intensity. The frequencies of secondary primary malignancies were not increased with the addition of elotuzumab to lenalidomide or bortezomib therapies. The frequency and severity of infections appeared similar among the treatment groups in Studies CA204004 (E-Ld versus Ld) and CA204009 (E-Bd versus Bd), particularly when adjusted for the different study drug exposure durations. The infections reported with elotuzumab in combination with lenalidomide or bortezomib were those expected for this patient population. The addition of elotuzumab did not appear to increase the rates or duration of infection.

Based on the safety data from 2 controlled, randomised, trials (CA204004 and CA204009), and other completed and ongoing studies, elotuzumab has demonstrated a favorable safety profile as demonstrated by the frequency and severity of AEs, SAEs, AEs leading discontinuation, and select AEs and in the context of the observed clinical efficacy in subjects who have received 1 or more prior therapies. The consistency of the elotuzumab safety results across trials underlines the reliability of the risk assessment provided by the sponsor.

First round benefit-risk assessment

First round assessment of benefits

The benefits of elotuzumab in the proposed usage are:

- In patients with relapsed or refractory multiple myeloma who receive a combination of elotuzumab, lenalidomide, and dexamethasone, a significant relative reduction of 30% in the risk of disease progression or death.
- In patients with relapsed or refractory multiple myeloma who receive a combination of elotuzumab, lenalidomide, and dexamethasone, overall response rate of 79%, compared to 66% with lenalidomide and dexamethasone.

First round assessment of risks

The risks of elotuzumab in the proposed usage are:

- Infusion reactions, including pyrexia, chills, and hypertension
- Lymphopenia

The safety profile of the elotuzumab combination therapy was similar to that of lenalidomide, thalidomide or bortezomib alone.

First round assessment of benefit-risk balance

The benefit-risk balance of Empliciti, in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received one to three prior therapies, is favourable.

There are insufficient data provided with regard to the clinical efficacy of the combination of Empliciti with bortezomib and dexamethasone, or the combination of Empliciti with thalidomide and dexamethasone to provide an assessment of benefit-risk. However, the safety profile of Empliciti combination therapy is similar to that of thalidomide or bortezomib alone.

First round recommendation regarding authorisation

Based on the clinical data submitted it is not recommended that the application for Empliciti (elotuzumab) as combination therapy for the treatment of multiple myeloma in adult patients who have received one or more prior therapies be approved.

However, it is recommended that the Empliciti (elotuzumab) be authorised to be used in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received one to three prior therapies.

Clinical questions

None

Second round evaluation

Details of sponsor's responses to clinical questions and evaluator's subsequent comments are contained in Attachment 2.

Second round benefit-risk assessment

Second round assessment of benefits

The evaluator notes the sponsor has provided an unsolicited update of efficacy (alone) in their Section 31 response. TGA does not accept efficacy data for evaluation unless specifically requested by the evaluator.

This additional data represents 18 months additional follow-up, pertaining to a later database lock (29 October 2015) as compared to that of the study in the dossier when originally submitted (19 February 2014).

Second round assessment of risks

The risks of elotuzumab for the proposed usage are unchanged, based upon the safety data presented with the dossier. No additional safety data for the additional 18 month follow-up period was presented in the Section 31 response. Therefore the evaluator cannot form a new opinion regarding risks of elotuzumab at this later database cut-off.

Second round assessment of benefit-risk balance

The risk-benefit balance cannot be established for the later database cut-off of 29 October 2015 since no additional safety data was presented. The efficacy *and* safety data pertaining to the database cut-off of 29 October 2015 will need to be presented to the TGA for full evaluation as a separate submission in the event that elotuzumab is registered on the ARTG.

Second round recommendation regarding authorisation

The following proposed indication remains suitable for registration:

> *Empliciti (elotuzumab) is indicated in combination with lenalidomide and dexamethasone for the treatment of multiple myeloma in adult patients who have received one to three prior therapies.*

V. Population pharmacokinetics

Study summary

The entire pharmacometric analysis is intended to support the registration of elotuzumab (BMS-901608) in subjects with MM.

A population pharmacokinetic (PPK) analysis of elotuzumab involving 375 subjects with MM was conducted by pooling data from four clinical studies: two Phase I studies (CA204005 and CA204007), one Phase II study (CA204011), and one Phase III study (CA204004). The PPK analysis was conducted to characterise elotuzumab serum concentration-time profiles in patients with MM and to determine the effect of key intrinsic and extrinsic covariates on elotuzumab PK parameters and exposure.

Using data from Study CA204004 an exposure-response (E-R) analysis for efficacy was performed to assess the relationship between elotuzumab exposure and efficacy, as measured by PFS in patients with relapsed or refractory MM who received elotuzumab in combination with lenalidomide and dexamethasone.

Using data from Study CA204004 E-R analyses for safety were performed to assess the relationship between elotuzumab exposure and safety in patients with relapsed or refractory MM who received elotuzumab in combination with lenalidomide and dexamethasone. Two endpoints were investigated in the safety analyses: time to first occurrence of Grade 3+ AEs; and time to AEs leading to discontinuation/death (excluding death due to disease progression).

Data from the initial PPK analysis involving 375 subjects (344 receiving lenalidomide/dexamethasone in combination with elotuzumab and 31 receiving elotuzumab monotherapy) was than combined with data from a Phase II study (CA204009) involving 74 subjects (all receiving bortezomib/dexamethasone in combination with elotuzumab). An external evaluation was performed to evaluate the previously developed elotuzumab PPK model and to assess the effect of co-administration of bortezomib/dexamethasone with elotuzumab on elotuzumab PK parameters.

The E-R PFS model of elotuzumab developed with data from Study CA204004 was then applied to Study CA204009 data and further developed to characterise the relationship between elotuzumab exposure and PFS in relapsed or refractory MM patients who were co-administered bortezomib/dexamethasone with elotuzumab.

Critical summary

Critical summary of key models

The key models, provided by the sponsor for the PPK studies in report CA204 and CA204009 were repeated using the software NONMEM version 7.3 and PsN version 3.7.6.

Only minor deviations from the submitted results for Study CA204 and for CA204009 of the modelling reports were found. The results submitted in the report can be confirmed according to the evaluation performed.

The models supplied were the final models found at the end of the model building process, however further model evaluation excluded some covariates (such as race and sex and B2-microglobulin) as not clinical significant. These were not removed from the final model. A model reflecting the conclusion of the report CA204 was not supplied.

A final model (retaining only clinically and statistically significant covariate-parameter relationships), a base model (no covariates), full model (all covariates tested) should have

been supplied as well and retested during this evaluation. See further comments on this below.

Due to the use of a newer estimation method available in NONMEM since version 7.3 by the sponsors (Monte Carlo expectation-maximisation method with importance sampling) slight deviations in parameter estimates found in repeating modelling runs are not unexpected.

A more detailed report can be found below. Results of the repeated PK model runs and result files have been submitted alongside this report.

Main comments are:

- The sponsor should clarify which covariates should be included in the final model and submit the true final model for report CA204 and report CA204009 for evaluation or adjust the report accordingly.
- The conclusion of report CA204 stated that:

  > *The following baseline covariates were not found to have clinically meaningful effects on the elotuzumab exposure: age, race, sex, renal function (as measured by eGFR), hepatic function, ECOG performance status, LDH, albumin, and β2-microglobulin.*

  Please clarify why the covariates: sex, race and β2-microglobulin were still included in the model carried forward to report CA204009?

Critical summary of the evaluation of report CA204

The sponsors report titled "Elotuzumab population pharmacokinetic and exposure – response analysis in relapsed or refractory multiple myeloma patients treated with elotuzumab with or without combination lenalidomide and dexamethasone" has been reviewed using the published guidelines,[17] which are adopted by TGA.

The report has been assessed on all points and has been found to agree or largely agree with the requirements outlined in the guidelines. A detailed critical summary, addressing each of the points, can be found below. Overall, the report was found to use appropriate data, method and evaluation standards for a PPK analysis.

Main comments are:

- There was no specific mention of how the pharmacokinetic predictions and covariate relationships generated by the PPK analysis might be used.
- 31 patients are reported to be on elotuzumab monotherapy; however, only 30 patients appear to be in the elotuzumab monotherapy study group (CA204011). The sponsor may wish to clarify exactly how many patients received elotuzumab monotherapy.
- The sponsor may also wish to clarify whether patients on elotuzumab monotherapy were generally on higher doses of elotuzumab than patients on lenalidomide/dexamethasone combination therapy.
- Omitting below lower limit of quantitation (BLQ) data is not the optimal way of handling such data and can lead to bias parameter estimates. Nevertheless, the BLQ data omission rate (5.2% of samples across the total PPK database) was reasonable low and such omission is unlikely to have a large impact on modelling outcomes.

[17] European Medicines Agency, "Guideline on Reporting the Results of Population Pharmacokinetic Analyses CHMP/EWP/185990/06)," 21 June 2007.

- Covariates to be tested for inclusion in the model and against which parameter were listed, however limited rationale for testing these covariates based on, for example, biological, pharmacological and/or clinical plausibility was provided; this is not in line with the EMA guidelines.
- Information regarding dropouts during the PPK analysis could not be found in the report.
- As pointed out by the sponsor shrinkage of the random effects was moderate, up to 41%. This is not unexpected from a data set with the majority of data coming from a Phase III study with relatively sparse sampling. Empirical Bayes estimate-based diagnostics (such as (IPRED)) should be interpreted with caution whenever substantial ETA shrinkage exists (usually greater than 20% to 30%).
- As pointed out by the sponsor the random effects on the peripheral volume were positively corrected with the initial target concentration in the peripheral compartment (RMAX) indicating difficulties in estimation of the parameters of the peripheral compartment.
- As pointed out by the sponsor the random effects on clearance were negatively correlated with the random effects on the Michaelis-Menten constant (KM) indicating difficulties in separation of non-specific and target mediated elimination pathways.
- It should be noted that the PK of elotuzumab has not been studied in patients with severe hepatic impairment, and the analysis included only one patient with moderate hepatic impairment.
- Hepatic impairment status and estimated glomerular filtration rate (eGFR) were considered to be time independent variables in this study.
- This study does not fully establish the differing effects of dexamethasone and lenalidomide usage on elotuzumab pharmacokinetic parameters although an effect from both agents is theorised in the discussion. The sponsor may wish to clarify whether all patients on combination therapy were on the same dexamethasone and lenalidomide dosages (that is, could either of these factors be examined as a continuous covariate in its own right).

Application of the PPK model and questions answered are considered reasonable. Conclusions drawn from the final models are valid and the results of the PPK model could be replicated in this assessment and were found appropriate.

Critical summary of the review of the PPK analysis

In study report CA2004009, data from the initial PPK analysis involving 375 subjects (344 receiving lenalidomide/dexamethasone in combination with elotuzumab and 31 receiving elotuzumab monotherapy) was combined with data from a Phase II study (CA204009) involving 74 subjects (all receiving bortezomib/dexamethasone in combination with elotuzumab). An external evaluation was performed to evaluate the previously developed elotuzumab PPK model and to assess the effect of co-administration of bortezomib/dexamethasone with elotuzumab on elotuzumab PK parameters.

This PPK analysis generally appeared appropriate and re-enforced findings made in the initial PPK analysis. Elotuzumab concentration-time data were well described by the prior model with correction for the effect of bortezomib/dexamethasone co-administration. Co-administration of lenalidomide/dexamethasone or bortezomib/dexamethasone resulted in a 35.5% (95% C.I.: 17.8-49.4%) or 50.7% (95% CI: 24.3-67.9%) decrease, respectively, in elotuzumab clearance relative to that seen in patients administered elotuzumab monotherapy. All other parameters of the updated model were within the 95% CI of the corresponding estimates of the final model from the initial PPK analysis.

Main comments are:

- While baseline covariates sex, race and β2-microglobulin were not found to have any clinically meaningful effects on elotuzumab exposure (see conclusions of initial PPK analysis (CA204)) these covariate effects remained incorporated into the final model tested in study report CA2004009. The sponsor may wish to justify why these covariate effects were retained.
- The entire modelling process was not repeated instead three different models were fitted to the combined data set. First, the final model of the earlier PPK analysis with fixed population parameters was applied. Then the same model was applied but the parameters of the model were re-estimated. Finally, additional effects were introduced that accounted for differences in elotuzumab clearance when elotuzumab is co-administered with lenalidomide/dexamethasone and bortezomib/dexamethasone and the model parameters were re-estimated.
- Limited rationale for testing usage of bortezomib/dexamethasone as a covariate based on, for example, biological, pharmacological and/or clinical plausibility, was provided; this is not in line with the EMA guidelines.
- Patients on elotuzumab monotherapy received a dose of 10mg/kg administered QW for two 28-day cycles followed by ten 28 day cycles with Q2W dosing. The original PPK analysis (CA204) suggests there are two patient cohorts on elotuzumab monotherapy one on 20mg/kg day and the other on 10 mg/kg day. The sponsor may wish to clarify how many patients received elotuzumab monotherapy and exactly what dosage regimen they received.
- 13% of samples from study CA204009 were excluded because they were BLQ. This is not the optimal way of handling such data and can lead to bias parameter estimates.
- No patients on the bortezomib/dexamethasone combination had severe hepatic impairment or renal failure.
- The sponsor may wish to clarify whether patients on elotuzumab monotherapy were generally on higher doses of elotuzumab than patients on lenalidomide/dexamethasone or bortezomib/dexamethasone combination therapy.

Critical summary of the exposure response analyses

Overall, the E-R analyses were performed appropriately and the analysis assumptions used and conclusions made are considered reasonable.

E-R analyses in MM patients treated with elotuzumab with or without combination lenalinomide and dexamethasone

In summary, the E-R analyses indicate that efficacy (PFS) appears to increase with increasing elotuzumab exposure, while risk of Grade 3+ AEs and risk of AEs leading to discontinuation or death does not increase with increasing elotuzumab exposures achieved with a 10 mg/kg dosing regimen.

No significant relationship was found between elotuzumab $C_{avg,SS}$ and PFS hazard ratio. Progression-free survival appears to increase as elotuzumab exposure increases over the range of exposures observed within a 10 mg/kg dosing regimen.

However, based on PPK analysis, VMAX is dependent on baseline serum M-Protein, resulting in elotuzumab exposure being lower in patients with high baseline serum M-Protein. Since the observation of an apparent E-R relationship between elotuzumab exposure and the risk of disease progression is confounded by baseline serum M-protein levels, no causal relationship can be established between low elotuzumab exposure and

higher risk for disease progression. No definite conclusions were drawn that higher steady-state exposure leads to a reduction in hazard for disease progression, indicating that both 10 and 20 mg/kg doses achieved maximum possible efficacy.

Main comments are:

- The relationship between exposure and reduction in disease progression should probably be evaluated further in future studies and post-marketing. The relationship between exposure and Grade 3+ AEs and AEs leading to discontinuation or death seems to be very weak, if at all existent. A higher dose should lead to higher exposure, which could potentially lead to increased PFS with limited consequences on safety. The sponsor should be asked what their post-marketing plans are to evaluate this further. Further, most patients in these studies received 10 mg/kg dosing regimen which limits the information gained from the range of observed exposures.

For all presented analyses the models and methods used and the covariate selection seem appropriate. The consequences and the impact of the final models have been discussed and are relevant in regards to clinical decision making, particularly in regards to influential covariates and dosing regimen selection.

E-R Analyses in MM patients treated with elotuzumab with or without combination bortezomib and dexamethasone

A smaller data set contributed to the E-R analyses performed for Study CA204009. No differences compared to the results reported in CA204 were found. The E-R analyses indicate that efficacy (PFS) appears to increase with increasing elotuzumab exposure with increasing elotuzumab exposures achieved with a 10 mg/kg dosing regimen.

The E-R analysis was performed appropriately and the analysis assumptions used and conclusions made are considered reasonable.

VI. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (EU-RMP) version 1 dated 11 June 2015 (data lock point 29 October 2014) with Australian Specific Annex (ASA) version 1 dated 29 July 2015, updated EU-RMP version 1.1 dated 10 December 2015, which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 2.

Table 2: Ongoing safety concerns.

Important identified risks	Infusion reaction
Important potential risks	None
Missing information	None

RMP evaluator comments

The sponsor has not provided compelling justification for omitting the safety concerns identified in clinical trials from the summary of safety concerns. Subject to the evaluation

outcomes of the nonclinical and clinical aspects of the Safety Specification, it is recommended that the sponsor add the following safety concerns identified in clinical trials in the ASA as important potential risks:

- Infections;
- Lymphopenia;
- Gastrointestinal toxicity;
- Second primary malignancies;
- Hepatotoxicity;
- Interference with determination of complete response.

Immunogenicity (important potential risk) and long term safety (missing information) are typical safety concerns related to newly developed humanised monoclonal antibodies. The sponsor should provide compelling justification to why they are unrelated to elotuzumab or add them to the ASA.

The following patient groups have not been studied in clinical trials. The sponsor should add them in the ASA as missing information:

- Use in patients with hepatic impairment;
- Use in patients with hepatitis infection;
- Use in patients with HIV infection;
- Use in pregnancy and lactation;
- Use in paediatric population.

Pharmacovigilance plan

Proposed pharmacovigilance activities

Routine pharmacovigilance activities[18] have been proposed to monitor the safety concern. No additional pharmacovigilance has been proposed by the sponsor.

RMP evaluator comments

The evaluator has noted that the US FDA has requested additional analyses as post-marketing commitments. The sponsor should update the ASA to include additional pharmacovigilance activities that are requested by overseas regulators or newly identified to address specific safety concerns. For activities that are not conducted in Australia, the sponsor should provide alternative plans or justify that the overseas activities are applicable to the Australian context.

The evaluator has noted the following statement in the EU-RMP:

- *Routine and additional PV activities will provide details of the types, frequency, severity, and outcome of the important identified risk.*
- *Routine and additional PV activities will provide information on any changes in the rate of occurrence, severity, and outcome of important identified risks as it relates to the established safety profile.*

[18] Routine pharmacovigilance practices involve the following: (a) All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner; (b) Reporting to regulatory authorities; (c) Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling; (d) Submission of Periodic Safety Update Reports (PSURs); and (e) Meeting other local regulatory agency requirements.

This is inconsistent with the sponsor's proposal that no additional pharmacovigilance is planned. The sponsor should clarify this inconsistency.

Risk minimisation activities

The sponsor has proposed routine[19] and additional risk minimisation to mitigate the risk of infusion reaction.

RMP evaluator comment

The sponsor's plan to use a combination of routine and additional risk minimisation is satisfactory.

- Potential for overdose

The sponsor states in the EU-RMP:

> *The potential for harm with overdose is low since elotuzumab is administered as an IV infusion in a hospital or clinic environment. In the integrated E-Ld and E-Bd studies, there were no reports of elotuzumab overdose. In completed clinical studies, doses > 22 mg/kg were considered an overdose.*
>
> *A single overdose of elotuzumab medication was administered in the ongoing Study CA204006, which did not result in clinical symptoms.*
>
> *The maximum tolerated dose of elotuzumab has not been determined. In the completed Phase 1 monotherapy studies some subjects received up to 20 mg/kg (highest total dose in mg) without apparent toxic effects.*
>
> *There is no known antidote for elotuzumab overdose. In case of overdose, patients should be closely monitored, and supportive treatment should be administered. Medication management of overdose should include customary supportive medical interventions aimed at correcting the presenting clinical manifestations.*

- Potential for transmission of infectious disease

The sponsor states in the EU-RMP:

> *Elotuzumab is manufactured according to Good Manufacturing Practice guidelines and the potential for transmission of infectious agents is low. Elotuzumab is not manufactured using any animal-derived products.*

- Potential for misuse for illegal purposes

The sponsor states in the EU-RMP:

> *Consistent with other immunomodulating agents, there is no evidence that suggests a risk for dependence on elotuzumab. Elotuzumab is administered by medical personnel in a hospital or clinic environment; therefore, the potential for misuse as a recreational drug is low.*

- Potential for off label use

The sponsor states in the EU-RMP:

> *The product label for elotuzumab will be carefully written to assure clarity regarding indications and contraindications.*
>
> *Use of elotuzumab in combination with lenalidomide in patients with newly diagnosed MM and no prior treatment is under active clinical development at BMS.*

[19] Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the PI or by careful use of labelling and packaging.

Considering that drugs administered in combination with elotuzumab are approved treatments for MM, concurrent use of elotuzumab with these drugs in a manner that is not in accordance with product information is possible once elotuzumab becomes a marketed product.

- Potential for paediatric off label use

The sponsor states in the EU-RMP:

Elotuzumab has not been studied in the paediatric population. The product label will be carefully written to assure clarity of indications and contraindications. The marketed indication will specify use in adults only and the product label will note that safety and efficacy in paediatric patients has not been established.

There is no relevant use of elotuzumab in the paediatric population in the intended indication.

RMP evaluator comment

The sponsor's analyses on the above issues are acceptable. It is reasonable to claim that paediatric patients are not the target population for the proposed indication. However, this does not prevent the product from being used for other oncology indications that are relevant to paediatric population. Therefore, the evaluator recommends that 'use in paediatric population' is added as missing information in the ASA.

Reconciliation of issues outlined in the RMP report

The following section summarises the first round evaluation of the RMP, the sponsor's responses to issues raised by the TGA RMP reviewer, and the RMP reviewer's evaluation of the sponsor's responses.

Recommendation #1 in RMP evaluation report

Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated Section 31 request and/or the nonclinical and clinical evaluation reports, respectively. It is important to ensure that the information provided in response to these includes consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.

Sponsor response

The applicant notes the RMP evaluator's request and wishes to provide the following information:

- The applicant has accepted the following recommendation by the clinical evaluator in relation to their assessment of benefit-risk and their recommendation for authorisation of this submission:
  - The benefit-risk balance of Empliciti, in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received one to three prior therapies, is favourable.
  - There are insufficient data provided with regard to the clinical efficacy of the combination of Empliciti with bortezomib and dexamethasone, or the combination of Empliciti with thalidomide and dexamethasone to provide an assessment of benefit-risk. However, the safety profile of Empliciti combination therapy is similar to that of thalidomide or bortezomib alone.

  Based on the clinical data submitted it is not recommended that the application for Empliciti (elotuzumab) as combination therapy for the treatment of multiple myeloma in adult patients who have received one or more prior therapies be approved.

However, it is recommended that the Empliciti (elotuzumab) be authorised to be used in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received one to three prior therapies.

- The nonclinical evaluator noted that the non-clinical program for elotuzumab, while adequate, had limited predictive value to guide the potential for reproductive toxicity and therefore recommended a number of amendments to the RMP and PI.

  The applicant acknowledges the recommendation, and this will be further considered at the time of the next update.

Evaluator's comment

The sponsor's response is noted.

Recommendation #2 in RMP evaluation report

The sponsor should provide an update to the market authorisation status overseas. Explanation should be provided for any decision of deferral, rejection, or withdrawal of an application. The sponsor should also provide the latest EU-RMP document that has been accepted by the EMA with an updated ASA.

Sponsor response

Elotuzumab received marketing authorisation approval from the FDA on 30 November 2015 for the following indication:

> *Empliciti is indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received one to three prior therapies.*

The CHMP adopted a positive opinion for approval of elotuzumab on the 29 January 2016 for the following indication:

> *Empliciti is indicated in combination with lenalidomide and dexamethasone for the treatment of multiple myeloma in adult patients who have received at least one prior therapy (sections 4.2 and 5.1).*

The most recently submitted EU RMP, Version 1.1 was accepted by the Rapporteur/Co-Rapporteur and is under review by the CHMP. A copy of Version 1.1 of the EU RMP dated 10 December 2015 is attached.

The applicant wishes to note that the following safety concerns are included in Version 1.1 of the RMP based on a request by the EMA:

- Important identified risks: infections and second primary malignancies
- Important potential risks: hypersensitivity and anaphylactic reaction
- Missing information: safety in patients with moderate and severe hepatic impairment & safety in patients of Asian race

The applicant does not consider the important potential risks or missing information necessary to ensure patient safety and proper use of the product based on available evidence; therefore, these safety concerns are not considered to be globally applicable.

Elotuzumab is currently approved in the US, and no other country.

The applicant commits to providing an updated ASA and will submit this to the PSMB following the ACPM meeting to ensure all changes from the second round evaluation and ACPM meeting are captured.

Evaluator's comment

The sponsor's response is noted. The sponsor's commitment to providing an updated ASA is satisfactory.

Recommendation #3 in RMP evaluation report

The approved indication in the US is:

> *Empliciti is indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received one to three prior therapies.*

The CHMP recommended indication is:

> *Empliciti is indicated in combination with lenalidomide and dexamethasone for the treatment of multiple myeloma in adult patients who have received at least one prior therapy.*

The evaluator would like to draw the Delegate's attention to the difference between these and the proposed indication in Australia.

Sponsor response

Please refer to the response to Recommendation 1. The applicant has accepted the recommendation by the clinical evaluator in relation to their assessment of benefit-risk and their recommendation for authorisation of this submission that aligns the proposed Australian indication with that approved by the FDA and for which the CHMP have adopted a positive opinion.

Evaluator's comment

The sponsor's response is noted. The sponsor's response to the clinical evaluator's recommendations is considered by the clinical evaluator and the TGA Delegate.

Recommendation #4 in RMP evaluation report

Subject to the evaluation outcomes of the nonclinical and clinical aspects of the Safety Specification, it is recommended that the sponsor add the following safety concerns identified in clinical trials to the ASA as important potential risks:

- Infections;
- Lymphopenia;
- Gastrointestinal toxicity;
- Second primary malignancies;
- Hepatotoxicity;
- Interference with determination of complete response.

Sponsor response

- Infections

Infections have been added as an identified risk to the EU RMP v1.1.

- Lymphopenia

The applicant proposes to monitor increased susceptibility to infections as a possible consequence of low lymphocyte count, rather than including lymphopenia as an important potential risk in the RMP.

Lymphopenia (any grade) as a laboratory value was reported in almost all subjects across the pooled clinical studies of elotuzumab in combination with lenalidomide and

dexamethasone (E-Ld) and elotuzumab in combination with bortezomib and dexamethasone (E-Bd) both in the elotuzumab and in the comparator arms. However, in Study CA204004, 1 Grade 3-4 lymphopenia was higher in the E-Ld group (244 subjects, 76.7%) compared with the Ld group (154 subjects, 48.7%). Lymphocyte count reductions occurred early in the study following administration of study drug. Therefore, lymphopenia is included as an adverse drug reaction (ADR) in the pertinent section of the Australian package insert (PI).

The difference in Grade 3-4 lymphopenia between treatment arms in Study CA204004 did not translate into a higher incidence rate of infections. In Study CA204004, the incidence rate of infections adjusted for exposure was comparable in the 2 treatment arms (incidence rate: 197 per 100 patient years in both treatment arms; see CA204004 CSR). Time to first infection (median time in months) was 2.3 in the E-Ld cohort and 2.7 in the Ld cohort (see CA204004 CSR), with a similar median absolute lymphocyte count at time of infection (0.7 versus 1.0 109/L (see CA204004 CSR)). Taken together, this data indicates that absolute lymphocyte count reduction in patients treated with elotuzumab was not a contributing factor to susceptibility to infection in Study CA204004.

· Gastrointestinal toxicity

The applicant does not consider gastrointestinal toxicity to be an important potential risk. Elotuzumab is an immunostimulatory humanised, IgG1 monoclonal antibody targeted against SLAMF7, a glycoprotein expressed on myeloma and NK cells. No SLAMF7 expression has been detected in colon, liver, pancreas, small intestine, spleen, stomach. Elotuzumab does not have a target in the gastrointestinal system.

In Study CA204004, events in the gastrointestinal disorders SOC were reported in 79.9% of subjects in the E-Ld arm compared to 67.2 % in the comparator arm. Severity grade 3 or higher events were reported in 9.7% of subjects in the E-Ld study arm and in 8.8 % of subjects in the comparator arm (see CA204004 CSR).1 Most frequently reported events in the gastrointestinal SOC were diarrhoea, constipation, nausea and vomiting (see CA204004 CSR). While the reported frequency of all of these events was slightly higher in the E-Ld study arm, the differences are small. Given the longer exposure to all three drugs in the E-Ld arm, the fact that the orally administered lenalidomide is associated with these events and the fact that this was a single blinded study, the differences are not considered to be clinically meaningful.

In summary, neither the SLAMF7 expression patterns, nor the clinical data support the addition of gastrointestinal toxicities to the list of important potential risks.

· Second primary malignancies

Second primary malignancies have been added as an identified risk to the EU RMP v1.1.

· Hepatotoxicity

The applicant does not consider the addition of hepatotoxicity in the list of important identified or potential risk necessary.

A single clinical trial subject met the criteria for Hy's law, aspartate aminotransferase (AST)/alanine aminotransferase (ALT) > 3 times the upper limit of normal (ULN), total bilirubin > 2 times ULN and alkaline phosphatase < 2 times the ULN, where a contribution of elotuzumab administration to the event could not be excluded. The subject had a history of hepatic steatosis prior to starting E-Ld. The event occurred more than 6 months after starting study therapy. The subject underwent a liver biopsy, which showed cirrhosis and evidence suggestive of drug-induced toxicity. Elotuzumab was permanently discontinued by the treating physician.

In CA204004, among the total 632 subjects with at least one ALT or AST assessment, 6 subjects (1.9%) in the E-Ld group (including the subject 4401-513 described above) and 2

(0.6%) in the Ld group had LFT values suggestive of potential drug induced liver injury (pDILI) (i.e., AST/ALT > 3 ULN and TBILI > 2 ULN and ALP < 2 ULN) (refer to Table S.7.4 in CA204004 CSR.

With the exception of the subject discussed above, all of the additional subjects in the E-Ld study group had plausible alternative explanations for the abnormal liver function tests. These explanations included cholelithiasis, cholangitis, porta hepatis tumour from myeloma progression, respiratory tract infection, and a subject with different events that contributed to the event and who were re-challenged with elotuzumab without recurrence of the event. A summary of liver laboratory test results by worst grade is provided.

Considering the longer exposure of subjects in the E-Ld study group compared to the subjects in the Ld study group, the small differences in liver parameter values between the groups do not indicate any untoward effect of elotuzumab administration on the liver.

Therefore the applicant considers the addition of hepatotoxicity in the list of important identified or potential risk unnecessary.

· Interference with determination of complete response

The applicant does not consider interference with determination of a complete response a safety risk.

As described in CA204004 CSR, interference underestimates the beneficial effect of elotuzumab administration. Hence, it should not be considered a potential risk.

Elotuzumab may be detected in the serum protein electrophoresis (SPEP) and serum immunofixation assays of myeloma patients and could interfere with correct response classification. A small peak in the early gamma region on SPEP that is IgGκ on serum immunofixation may potentially be attributed to elotuzumab, particularly in patients whose endogenous myeloma protein is IgA, IgM, IgD, or lambda light chain restricted. This interference can impact the determination of complete response and possibly relapse from complete response in patients with IgG kappa myeloma protein.

Evaluator's comment

The sponsor has added infections and second primary malignancies as identified risks to the updated RMP. The sponsor has provided reasonable justification to the risk of gastrointestinal toxicity, hepatotoxicity, and interference with determination of complete response. The sponsor is also committed to monitor the increased susceptibility to infections as a possible consequence of low lymphocyte count. These are acceptable.

Recommendation #5 in RMP evaluation report

Immunogenicity (important potential risk) and long term safety (missing information) are typical safety concerns related to newly developed humanised monoclonal antibodies. The sponsor should provide compelling justification to why they are unrelated to elotuzumab or add them to the ASA.

Sponsor response

In Study CA204004, the impact of elotuzumab ADA in subjects with infusion or hypersensitivity reactions following elotuzumab treatment was assessed (see CA204004 CSR). In this study, 116 subjects, who had evaluable baseline and at least one post-baseline ADA assessment, when treated with E-Ld, experienced hypersensitivity or infusion reactions (based on SMQ narrow definition). Among these 116 subjects, 21 (18.1%) and 95 (81.9%) subjects were ADA-positive and ADA-negative, respectively. Of these 116 subjects with infusion or hypersensitivity reactions, 10 were neutralising antibody (NAb) positive subjects. In comparison, 88 subjects when treated with lenalidomide/dexamethasone alone (control arm) experienced hypersensitivity reactions. None of the subjects in the control arm had infusion reactions (see CA204004 CSR). No

definite conclusions can be made regarding the temporal relationship of detection of ADAs and hypersensitivity or infusion reactions.

Additionally, in the majority of the ADA positive subjects, immunogenicity started early, was transient, and resolved by 2 to 4 months; thus it lasted for 2 to 3 months in only 2 subjects. No clear association can be established between presence of ADA and loss of efficacy ADA positive versus BOR and PFS).

Furthermore, the safety profile in the 19 subjects who were Nab positive was not different when compared to ADA negative subjects (see CA204004 CSR). In summary, there is no evidence that the immunogenicity had clinically meaningful impact on the safety of elotuzumab.

Evaluator's comment

The sponsor has provided reasonable justification. Therefore, the sponsor's response is acceptable.

Recommendation #6 in RMP evaluation report

The following patient groups have not been studied in clinical trials. The sponsor should add them to the ASA as missing information:

- Use in patients with hepatic impairment;
- Use in patients with hepatitis infection;
- Use in patients with HIV infection;
- Use in pregnancy and lactation;
- Use in paediatric population.

Sponsor response

- Use in patients with hepatic impairment

The applicant acknowledges that, "safety in patients with moderate and severe hepatic impairment" is included in the EU-RMP v1.1 (dated 10 December 2015) as missing information. This inclusion was mandated by EMA and the applicant does not consider this safety concerns to be globally applicable.

Patients with hepatic impairment are commonly excluded from clinical trials. The lack of information with elotuzumab due to their exclusion from Study CA204004 should not affect the treatment or management of disease of these patients.

Elotuzumab is an IgG1 monoclonal antibody, which is likely eliminated via several pathways similar to that of other antibodies. Hepatic excretion is not expected to play a relevant role in the excretion of elotuzumab.

Therefore, the applicant considers the addition of these patients in the list of missing information for this condition unnecessary.

- Use in patients with hepatitis infection

Patients with a known history of, or documented positive hepatitis B or C, are commonly excluded from clinical trials. The lack of information with elotuzumab due to their exclusion from Study CA2040041 should not affect the treatment or management of disease of these patients.

Therefore, the applicant considers the addition of these patients in the list of missing information for this condition unnecessary.

- Use in patients with human immunodeficiency virus (HIV) infection

Patients with HIV are commonly excluded from multiple myeloma clinical trials since they represent a small percentage of the multiple myeloma patient population and usually have a prognosis that prevents their inclusion in clinical research. The lack of information with elotuzumab due to their exclusion from Study CA204004 should not affect the treatment or management of disease of these patients. Therefore, the applicant considers the addition of patients with HIV in the list of missing information for this condition unnecessary.

· Use in pregnancy and lactation

Elotuzumab in combination with lenalidomide is contraindicated in females who are pregnant, because of the risk of foetal harm associated with lenalidomide, a thalidomide analogue. In addition, multiple myeloma is a disease of advanced age. Therefore, the applicant does not consider use in pregnancy and lactation as "missing information".

· Use in paediatric population (see RMP evaluator comment)

The applicant does not consider the paediatric population as "missing information". There is no use of elotuzumab in the paediatric population in the intended indication, and there is no other indication for elotuzumab. In the European Union multiple myeloma is one of the conditions that is under the scope of a class waiver under Regulation EC No. 1901/2006 as it occurs in adult population only. Therefore, a paediatric investigation plan for elotuzumab is not mandatory in the EU.

The product label will be carefully written to assure clarity of indications and contraindications. The marketed indication will specify use in adults only and the product label will note that safety and efficacy in paediatric patients has not been established.

Evaluator's comment

The sponsor has added 'use in patients with hepatic impairment' as missing information in the EU-RMP. The sponsor has advised that it had changed the proposed indication to use in combination with lenalidomide. It is acceptable that use in pregnancy is not relevant in this context as it is a contraindication. The sponsor has provided reasonable justification to the issue of use in patients with hepatitis, HIV and use in paediatric population.

Recommendation #7 in RMP evaluation report

The evaluator has noted that the US FDA has requested additional analyses as post-marketing commitments. The sponsor should update the ASA to include additional pharmacovigilance activities that are requested by overseas regulators or newly identified to address specific safety concerns. For activities that are not conducted in Australia, the sponsor should provide alternative plans or justify that the overseas activities are applicable to the Australian context.

Sponsor response

Additional pharmacovigilance activities have not been required of the applicant as a condition of approval by any health authority nor has the applicant committed to perform any activities to address specific safety concerns at the request of overseas regulators. However, as described in the approval letter issued by FDA on 30 November 2015, the applicant has the following postmarketing commitment (unrelated to pharmacovigilance) in the United States:

Conduct an elotuzumab exposure-response analysis for efficacy and safety utilizing data from trial CA204006. The result of the exposure-response analyses from both CA204004 and CA204006 will be used to determine whether a post-marketing trial is needed to optimize the dose in patients with multiple myeloma who have low exposure to elotuzumab at the approved dose (10 mg/kg). Submit a final report of the exposure-response analyses based on CA204004 and CA204006.

Evaluator's comment

The evaluator has noted the sponsor's clarification. The sponsor's response is satisfactory.

Recommendation #8 in RMP evaluation report

The evaluator has noted the following statement in the EU-RMP:

- *Routine and additional PV activities will provide details of the types, frequency, severity, and outcome of the important identified risk.*
- *Routine and additional PV activities will provide information on any changes in the rate of occurrence, severity, and outcome of important identified risks as it relates to the established safety profile.*

This is inconsistent with the sponsor's proposal that no additional pharmacovigilance is planned. The sponsor should clarify this inconsistency.

Sponsor response

The applicant acknowledges that the RMP evaluator is correct in highlighting this inconsistency. All activities proposed are routine activities.

Evaluator's comment

The sponsor's response is satisfactory.

Recommendation #9 in RMP evaluation report

This additional risk minimisation proposal is incomplete. Although the sponsor has provided the content of the risk minimisation activity, there is no detail on how the activity will be implemented. The sponsor has proposed in the EU-RMP:

> *Routine and additional PV activities will provide information on any changes in the rate of occurrence, severity, and outcome of important identified risks as it relates to the established safety profile.*

This is a proposal to measure outcome indicators. It should be noted that the effectiveness of the additional risk minimisation depends on the effective implementation of premedication. It is recommended that the sponsor revise the ASA to include the following:

· How will the activity be implemented? The sponsor should provide details on how it plans to ensure premedication is administered as recommended, for example, a controlled access system to ensure only patients who have been pre-medicated can proceed with elotuzumab therapy;

· How will the effectiveness of the implementation process be measured?

Sponsor response

· How will the activity be implemented?

EU-RMP v1.0 (dated 11 June 2015) was submitted to TGA with the initial application. An updated EU-RMP v1.1 (dated 10 December 2015) is included with this Response to RMP Evaluation Report Round 1.

In EU-RMP v1.0, premedication is included as an additional risk minimisation activity. In EU-RMP v1.1, premedication is now considered by the applicant to be routine risk minimization because this mandatory premedication for the important identified risk of infusion reaction, is included in the label (Australian PI).

This mandatory premedication requirement included in the Australian PI will provide the prescriber with detailed and easy to follow instructions regarding the precise dose and timing of the premedication regimen.

It should be noted that premedication is considered standard clinical practice and prescribers of elotuzumab will be familiar with treating patients with biological drugs, which carry risks of infusion reactions and thus most require premedication.

- How will the effectiveness of the implementation be measured?

Effectiveness of this routine risk minimisation activity will be measured as described in EURMP v1.1 (dated 10 December 2015).

Evaluator's comment

The evaluator has noted that premedication has been changed from additional risk minimisation to routine risk minimisation in the EU-RMP version 1.1. This is satisfactory.

The sponsor has advised in the EU-RMP that the effectiveness of risk minimisation activities will be measured by 'routine and additional PV activities'. Since the sponsor has confirmed in its response to the TGA recommendation that there is no additional pharmacovigilance proposed for this product, it is assumed that the risk minimisation activity will be measured through routine pharmacovigilance alone. The evaluator considers that routine pharmacovigilance is adequate to evaluate the effectiveness of routine risk minimisation through PI.

Recommendation #10 in RMP evaluation report

In regard to the proposed routine risk minimisation activities, the US approved product label contains the following warnings on 'second primary malignancies', 'hepatotoxicity' and 'interference with determination of complete response' under 'warnings and precautions'. In comparison, the draft Australian PI contains information on interference with assays under 'clinical trials'. It is recommended to the Delegate that these warnings are added to the PI under 'precaution' to improve patient safety.

- In a clinical trial of patients with multiple myeloma (N = 635), invasive second primary malignancies (SPM) have been observed in 9.1% of patients treated with E-Ld and 5.7% of patients treated with Ld. The rate of hematologic malignancies were the same between E-Ld and Ld treatment arms (1.6%). Solid tumours were reported in 3.5% and 2.2% of E-Ld-and Ld-treated patients, respectively. Skin cancer was reported in 4.4% and 2.8% of patients treated with E-Ld and Ld, respectively. Monitor patients for the development of second primary malignancies.
- Elevations in liver enzymes (aspartate transaminase/alanine transaminase [AST/ALT] greater than 3 times the upper limit, total bilirubin greater than 2 times the upper limit, and alkaline phosphatase less than 2 times the upper limit) consistent with hepatotoxicity were reported in 2.5% and 0.6% of E-Ld-and Ld-treated patients in a clinical trial of patients with multiple myeloma (N = 635). Two patients experiencing hepatotoxicity were not able to continue treatment; however, 6 out of 8 patients had resolution and were able to continue treatment. Monitor liver enzymes periodically. Stop Empliciti upon Grade 3 or higher elevation of liver enzymes. After return to baseline values, continuation of treatment may be considered.
- Empliciti is a humanised IgG kappa monoclonal antibody that can be detected on both the serum protein electrophoresis (SPEP) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein. This interference can impact the determination of complete response and possibly relapse from complete response in patients with IgG kappa myeloma protein.

Sponsor response

The applicant agrees that SPMs should be added to the "Precautions" section of the PI and has provided language for this in the draft PI revisions sent to TGA with this response. The sponsor does not agree that hepatotoxicity should be added to the "Precautions" section of

the PI as this adverse event is not considered to be a potential or identified risk related to Empliciti treatment.

The applicant agrees to add Empliciti interference with determination of complete response to the section entitled "Interactions with Other Medicines" as this is not a safety issue for "Precautions", but rather a possible interference with determination of the effectiveness of Empliciti.

Evaluator's comment

The evaluator has noted the sponsor's response. The recommendations remain for the TGA Delegate's determination.

Recommendation #11 in RMP evaluation report

It is reasonable to claim that paediatric patients are not the target population for the proposed indication. However, this does not prevent the product from being used for other oncology indications that are relevant to paediatric population. Therefore, the evaluator recommends that 'use in paediatric population' is added as missing information in the ASA.

Sponsor response

The applicant does not consider the paediatric population as "missing information". There is no use of elotuzumab in the paediatric population in the intended indication, and there is no other indication for elotuzumab. In the European Union multiple myeloma is one of the conditions that is under the scope of a class waiver under Regulation EC No. 1901/2006 as it occurs in adult population only. Therefore, a paediatric investigation plan for elotuzumab is not mandatory in the EU.

The product label will be carefully written to assure clarity of indications and contraindications. The marketed indication will specify use in adults only and the product label will note that safety and efficacy in paediatric patients has not been established

Evaluator's comment

The sponsor's response is acceptable.

Summary of recommendations

Outstanding issues

Issues in relation to the RMP

- The recommendations on the draft PI and CMI remain, awaiting consideration by the Delegate.
- Recommendation from nonclinical evaluation report: The sponsor should incorporate the recommended changes made by the nonclinical evaluation report in the updated ASA.

Comments on the safety specification of the RMP

Clinical evaluation report

The Prescription Medicines Authorisation Branch of TGA has provided the following comments in the clinical evaluation report:

> *The Safety Specification in the draft RMP is satisfactory.*

Nonclinical evaluation report

The Scientific Evaluation Branch of the TGA has provided the following comments in the nonclinical evaluation report:

While the results and conclusions drawn from individual studies detailed in the sponsor's draft RMP are in general concordance with those of the nonclinical evaluator, the overall conclusion on the nonclinical program is considered to be misleading. The nonclinical program for elotuzumab, while adequate, has limited predictive value, with many aspects of the safety profile remaining poorly characterised. A notable example is the potential of elotuzumab to adversely affect embryofoetal development. Reproductive toxicity studies have not been conducted for elotuzumab (which is acceptable), but consideration of the pharmacological activity of the compound, and additionally its transfer across the placenta, does give rise to concerns for effects on the developing foetus. It is recommended that the section which suggests that no nonclinical safety concerns exist for the drug and that the toxicity of the drug has been comprehensively investigated be removed. Thus:

Because of the limitation in species specific cross reactivity and the lack of a relevant animal species or a valid transgenic mouse model in which to conduct toxicological studies, the nonclinical safety package consists primarily of in vitro (tissue cross reactivity, human whole blood and bone marrow assays) and limited in vivo assessments to address the selectivity and potential toxicity of elotuzumab. The scope and results of the nonclinical toxicity studies are sufficient to support the clinical use of IV elotuzumab at the proposed doses and dosing regimen in advanced cancer, but they are unable to robustly characterise the toxicity profile of the drug, including its potential for embryofoetal harm.

RMP evaluator comment

The sponsor has provided the following response to the recommendations:

The applicant acknowledges the recommendation, and this will be further considered at the time of the next update.

This is acceptable. The sponsor should incorporate the recommended changes in the updated ASA.

Key changes to the updated RMP

In their response to the TGA Section 31 Requests the sponsor provided an updated EU-RMP version 1.1 dated 10 December 2015. Key changes from the version evaluated at Round 1 are summarised below.

Table 3: Key changes to RMP versions.

Safety specification	The following safety concerns have been added to the summary of safety concerns: · Important identified risks: infection, second primary malignancies; · Important potential risks: hypersensitivity and anaphylactic reaction; · Missing information: safety in patients with moderate and severe hepatic impairment, safety in patients of Asian race.
Pharmacovigilance activities	Routine pharmacovigilance has been added to monitor all the newly added safety concerns.
Risk minimisation activities	Premedication has been changed from additional risk minimisation to routine risk minimisation in the EU-RMP.

RMP evaluator's comments

The evaluator has no objection to the above changes and recommends to the Delegate that the updated version is implemented.

Suggested wording for conditions of registration

RMP

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

The suggested wording is:

> *Implement EU-RMP version 1.1 dated 10 December 2015 (data lock point 29 October 2014) with Australian Specific Annex version 1 dated 29 July 2015 and any future updates as agreed by the TGA as a condition of registration.*

VII. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The biochemistry and Infectious disease safety assessments were completed to the satisfaction of the evaluators.

Nonclinical

The nonclinical evaluator noted the limited nature of the nonclinical studies presented in the dossier, in particular owing to the lack of an appropriate animal model, and that "the safety assessment will chiefly rely on clinical data".

Of note, in human bone marrow culture, elotuzumab had "no significant effect on haemopoietic progenitor proliferation".

There was no objection to the registration of elotuzumab for the proposed usage in patients with multiple myeloma. Pregnancy Category C was proposed and supported.

The nonclinical evaluator recommended a number of PI changes which have all been adopted by the sponsor.

Clinical

Pharmacology

Elotuzumab exhibits nonlinear pharmacokinetics consistent with target-mediated clearance, consistent with other monoclonal antibody therapies.

Clearance is estimated to be 17.5 (21.2%) to 5.8 (31%) mL/day/kg with an increase in dose from 0.5 (i.e., 0.05 times the recommended dosage) to 20 mg/kg.

Following steady-state, approximately 97% elotuzumab is cleared within 82.4 days (CV 48%).

No pharmacodynamic assessments were performed in the pivotal study of efficacy and safety which is described below.

PSC advice

The PSC advised that further elucidation of the relationship between M-protein or exposure (and possible other factors) and disease progression may be required. The delegate could consider requesting the provision of Studies CA204004 and CA204006 which were not provided with the submission dossier. The Delegate should consider the extent to which the sponsor should be required to undertake further studies of the exposure response relationship.

Efficacy

- Study CA204004 was a Phase III, Randomized, Open Label Trial of Lenalidomide/Dexamethasone With or Without Elotuzumab in Relapsed or Refractory Multiple Myeloma.

Primary objective:

- To compare PFS of lenalidomide/low-dose dexamethasone + elotuzumab (E-Ld) versus lenalidomide/low-dose dexamethasone (Ld) in subjects with relapsed or refractory multiple myeloma (MM).
- To compare the ORR of E-Ld versus Ld.

Secondary outcomes:

- To compare overall survival of E-Ld versus Ld.
- To compare the change from baseline of the mean score of pain severity and the change from baseline of the mean score of pain interference using the Brief Pain Inventory- Short Form (BPI-SF) of E-Ld versus Ld.

Prior treatments and reasons for their discontinuation are seen below. A deficiency of the study is there were eleven patients who had not received prior treatment who were randomised. The proportion in each arm, though discrepant, is not likely to materially affect the overall study outcomes.

Table 4: End of Treatment Summary - All Randomised Subjects.

	E-Ld	Ld	Total
Subjects randomized [a]	321	325	646
Subjects never treated	2 (0.6)	9 (2.8)	11 (1.7)
Subjects treated	319 (99.4)	316 (97.2)	635 (98.3)
Subjects still on treatment [b]	113 (35.4)	66 (20.9)	179 (28.2)
Subjects off treatment	206 (64.6)	250 (79.1)	456 (71.8)
Reason off treatment [b]			
Disease progression	135 (42.3)	149 (47.2)	284 (44.7)
Study drug toxicity	28 (8.8)	42 (13.3)	70 (11.0)
Adverse event unrelated to study drug	15 (4.7)	26 (8.2)	41 (6.5)
Subject request to discontinue study treatment	20 (6.3)	13 (4.1)	33 (5.2)
Subject withdrew consent	4 (1.3)	8 (2.5)	12 (1.9)
Other	1 (0.3)	10 (3.2)	11 (1.7)

	E-Ld	Ld	Total
Death	1 (0.3)	1 (0.3)	2 (0.3)
Subject no longer meets study criteria	2 (0.6)	0	2 (0.3)
Poor/non-compliance	0	1 (0.3)	1 (0.2)

All randomized subjects, by treatment arm as randomized. Percentages based on treated subjects. There was 1 subject randomized to treatment E-Ld but who received treatment Ld.

Baseline demographics were generally balanced between the treatment arms

A similar proportion of patients in each arm were refractory or relapsed. Of note, patients were excluded from study entry if they were refractory to lenalidomide as their most recent line of therapy.

Tumour assessments were performed every 4 weeks. Primary efficacy assessments were per independent review.

At a median duration of follow-up of 24 months, the estimate of median PFS in the elotuzumab exposed-group was 19.4 months (95% CI, 16.6 to 22.2) versus 14.9 months (95% CI, 12.1 to 17.2) in the control group. Of note, following this duration of follow-up, there remains only 133/646 (20.1%) of the study population evaluable.

Subgroup analyses did not demonstrate any groups who may not obtain a similar degree of benefit from the study population as a whole. The only exceptions were the patients identified as having T(14:16) or T(14:20), however, the number of patients in these groups are not sufficient to draw any firm conclusions.

At dossier submission, the OS data was immature. The clinical evaluator considered that elotuzumab could be registered on the basis of the PFS data alone. In their Section 31 response, the sponsor included an unsolicited interim analysis of OS, with proposed amendments to the PI. Given the unsolicited nature of the efficacy data and lack of accompanying safety update, it was not accepted for evaluation.

The difference in objective response rate, by independent review, was 12.6% (95% CI 6.1, 19.2) favouring the elotuzumab arm.

Quality of life assessments were performed using the non-disease specific tool EROTC-QLQ-C30 and the multiple myeloma specific tool EORTC-QLQ-MY20. In addition, the Brief Pain Inventory was utilised.

No significant worsening of patient symptoms in the elotuzumab treatment arm was observed for any of the assessment tools, indicating similarity of patient experience with either E-Ld or Ld.

Studies CA204009 & Study HuLuc63-1702

These were Phase Ib/II and 2 studies of the efficacy and safety of elotuzumab in combination with bortezomib and dexamethasone in comparison with bortezomib and dexamethasone in patients with RRMM.

These studies were considered by the clinical evaluator to be insufficient to recommend registration of elotuzumab in combination with bortezomib. The sponsor has concurred and amended to proposed indication, and product information, accordingly.

Study HuLuc63-1703

This dose response study demonstrated comparable efficacy between patients exposed to 10 mg/kg and 20 mg/kg elotuzumab. Median duration of PFS and response was longer for those receiving 10 mg/kg (the proposed dose for registration).

Safety

Exposure

The safety of elotuzumab has been assessed across completed studies of monotherapy and in combination with other agents for the treatment of multiple myeloma, totalling 619 patients. In ongoing studies, the sponsor reported outcomes from 440 patients.

Deaths and serious AEs

Deaths were less common in the pivotal study among patients receiving elotuzumab (29.6% versus 36.6% placebo).

No deaths were reported from Study CA 204005, CA204007.

Pneumonia was more commonly observed in those patients exposed to elotuzumab in the pivotal study (14.2% versus 9.5% placebo)

Herpes zoster infection was also more commonly observed among those exposed to elotuzumab.

Peripheral neuropathy of any grade occurred in 14.2% of the elotuzumab arm of the pivotal study and 8.2% of the placebo arm. Grades 3-5 of peripheral neuropathy were of similar incidence.

Deep vein thrombosis of any grade, and Grades 3-5, were commoner in the elotuzumab arm (7.2% and 5.7%, respectively) as compared to placebo (3.8% and 2.2%, respectively)

Discontinuations

In the pivotal study, there was a similar incidence of subjects who discontinued one or more study treatment due to an AE (12.9% in E-Ld and 14.8% in Ld).

Dose modifications

In the pivotal study, elotuzumab dose delays occurred in 58.5% of patients with 32% requiring more than one delay.

Table 5: Dose delays.

	E-Ld N = 318
NUMBER OF SUBJECTS WITH AT LEAST ONE DELAY	186 (58.5)
NUMBER OF DELAYED ADMINISTRATIONS	
1	83 (26.1)
2	38 (11.9)
3	31 (9.7)
>=4	34 (10.7)
REASON FOR DELAY	
HEMATOLOGIC TOXICITY	2 (0.6)
NON-HEMATOLOGIC TOXICITY	3 (0.9)
ADVERSE EVENT	52 (16.4)
DOSING ERROR	3 (0.9)
OTHER	156 (49.1)
UNKNOWN	18 (5.7)

Reason UNKNOWN is reported when there is a derived delay and no reason is being reported on the CRF. Subjects may have more than one reason for delay.

Elotuzumab omission occurred in 55.3% of patients with 28% requiring more than one omission.

Table 6: Dose omissions.

	E-Ld N = 318
NUMBER OF SUBJECTS WITH AT LEAST ONE OMISSION	176 (55.3)
NUMBER OF OMITTED ADMINISTRATIONS	
1	87 (27.4)
2	48 (15.1)
3	21 (6.6)
>=4	20 (6.3)
REASON FOR OMISSION	
HEMATOLOGIC TOXICITY	4 (1.3)
NON-HEMATOLOGIC TOXICITY	8 (2.5)
ADVERSE EVENT	132 (41.5)
DOSING ERROR	5 (1.6)
OTHER	59 (18.6)
UNKNOWN	9 (2.8)

Reason UNKNOWN is reported when there is a derived omission and no reason is being reported on the CRF. Subjects may have more than one reason for omission.

Most patients did not require interruption of elotuzumab administration (87.1%); the commonest reason for interruption being an infusion reaction.

Table 7: Dose interruptions.

	E-Ld N = 318
NUMBER OF SUBJECTS WITH AT LEAST ONE INFUSION INTERRUPTION	41 (12.9)
NUMBER OF INFUSION INTERRUPTIONS	
1	30 (9.4)
2	9 (2.8)
3	1 (0.3)
>=4	1 (0.3)
REASON FOR INFUSION INTERRUPTION	
INFUSION REACTION	15 (4.7)
INFUSION ADMINISTRATION ISSUES	14 (4.4)
OTHER	16 (5.0)

Subjects may have more than one reason for infusion interruption.

Common AEs

Haematological AEs occurred across lineages – lymphopaenia, anaemia, thrombocytopaenia and neutropaenia – the most common being lymphopaenia.

Infusion related reactions were observed across all studies, with suitable advice for their prevention in the PI.

Other notable AEs include diarrhoea, fatigue and muscle spasms, and back pain.

AEs of interest

Infusion reactions

The incidence of infusion reactions was 33/318 (10.4%) of the pivotal study population receiving elotuzumab. The majority of reactions occurred in the first two cycles of treatment. Two patients discontinued elotuzumab owing to an infusion reaction. The incidence of an infusion reaction did not appear to be related to the rate of infusion or the age of the patient.

Infections

The incidence of infections (all grades or Grades 3-5) was higher in elotuzumab exposed patients.

Although there were only two events of atypical pneumonia, owing to the neutropenogenic and lymphopenogenic effects of elotuzumab, there is an ongoing risk of atypical infections in patients receiving it. This risk should be included in the PI.

Second malignancies

The incidence of second primary (solid tumours and non-melanoma skin cancers) malignancies was higher among those exposed to elotuzumab. This risk has been added to the PI.

ECG

No significant effects on QT/QTc interval were observed in the subset of patients with evaluable ECGs.

Immunogenicity

The incidence of persistent anti-drug antibodies was low in the across studies of combination use with lenalidomide or bortezomib (2 patients). Transient anti-drug antibodies were detected in 18% of patients across studies. No pharmacodynamic assessment was performed for the pivotal study to assess the impact on efficacy.

From the pivotal study CSR, two patients were reported to have Grade 3 atypical pneumonia (0.6%).

Safety in special populations

There is limited data regarding the safety of patients with renal or hepatic impairment. The PI reports the outcomes from a total of 26 patients with varying degrees of renal impairment.

No patients with moderate or severe degrees of hepatic impairment have been studied.

Risk management plan

The RMP proposed by the sponsor was considered generally acceptable by the TGA's evaluation.

The RMP evaluator recommended amendments to the PI to be considered by the Delegate.

The RMP Evaluator recommends the following RMP-related condition of registration:

Implement EU-RMP version 1.1 dated 10 December 2015 (data lock point 29 October 2014) with ASA version 1 dated 29 July 2015 and any future updates as agreed by TGA as a condition of registration

Risk-benefit analysis

Delegate's considerations

Efficacy

The data presented in the original dossier demonstrates a clinically and statistically significant benefit from the combination of elotuzumab, lenalidomide and dexamethasone over lenalidomide plus dexamethasone. This is shown by the hazard ratio of progression-free survival of 0.68 (95% CI 0.55, 0.85), p = 00001, equating to an improvement in duration of median PFS of 4.5 months.

Efficacy endpoints were based on serum and urine M-protein, corrected calcium, and bone marrow assessments at pre-defined intervals – these are consistent with the diagnostic and response criteria for multiple myeloma. It is notable that the efficacy of elotuzumab was not substantially different among a number of sub-groups which have been associated with poorer outcomes, that is, cytogenetic sub-groups (including t(4:14), t(14:16) and del17p), baseline B2 microglobulin concentration, degree of renal impairment and 'high-risk' categorisation.

Safety

The safety profile of elotuzumab has been reported from a sufficient number of patients, including from randomised and non-randomised studies to warrant registration.

The safety profile is sufficiently characterised in the PI, except for a statement regarding the potential for atypical infections, given the mechanism of action of elotuzumab & concomitant administration of dexamethasone.

In contrast to the pre-clinical finding in bone marrow culture of no effect upon progeny, the clinical data demonstrated effects on red, white and platelet cell lines.

RMP

The Delegate notes sponsor has updated the RMP to address the advice of the Advisory Committee on the Safety of Medicines (ACSOM) that the initial summary of safety concerns was considered inadequate.

ACSOM identified the potential for incorrect dose administration since the draft PI states that the 300 mg and 400 mg vials of elotuzumab contain 340 mg or 440 mg elotuzumab respectively, whereas the Presentation section of the draft PI mentions only the 340 mg or 440 mg quantities of lyophilized powder. The sponsor should address this issue in their pre-ACPM response.

ACSOM recommended "consideration should be given to reflecting the adverse event profiles of the combination therapies in the PI". The Delegate considers the risks of elotuzumab may be specific to the single regimen in which it is proposed to be registered. The draft PI states in the "interactions with other medicines" section, that pharmacokinetic studies have not been conducted. If future submissions employ a different regimen of an elotuzumab-containing regimen, then accordingly, the PI will need updating at that time.

Outstanding issues for the consideration of the Delegate raised by the second round RMP evaluation:

- The Delegate concurs with the advice of ACSOM which recommended that "hepatotoxicity" be added to the Precautions section of the PI. The product information should contain the same wording as the FDA label for this precaution. The sponsor's explanation that in regard to hepatotoxicity "this event is not considered to be a potential or identified risk related to Empliciti treatment" is not supported by the randomised controlled trial data.
- The Delegate disagrees with the sponsor's proposal to include a statement regarding the potential interference of the assays used to assess treatment response in the "interactions with other medicines" section of the PI. This effect is not a result of interaction with any other registered medicines. Prescribers should be warned of the potential for inaccurate efficacy assessments in the Precautions section.

Dose

The proposed dose is considered appropriate. The clinical evaluator states the dose of 10 mg/kg was sufficient to saturate the CS2 target on multiple myeloma cells in bone marrow and trough concentration was greater than to obtain efficacy in pre-clinical models.

Indication

The sponsor initially proposed an indication which reflected the combination of elotuzumab and either lenalidomide or bortezomib.

The clinical evaluator proposed an indication at the first round of evaluation, solely in combination with lenalidomide/dexamethasome, which was adopted by the sponsor:

> *Empliciti (elotuzumab) is indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received one to three prior therapies.*

However, the Delegate considers that this proposed indication would preclude use in patients who have received more than three prior therapies; such patients may obtain an efficacy benefit. The Delegate therefore proposes:

> *Empliciti (elotuzumab) is indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.*

Summary of issues

Satisfactory efficacy has been demonstrated in patients with relapsed/refractory multiple myeloma receiving lenalidomide and dexamethasone

There is insufficient efficacy to warrant registration of elotuzumab in combination with bortezomib and dexamethasone

Adverse events of infusion reaction, infections (pneumonia), second primary malignancy, peripheral neuropathy, hepatotoxicity and thromboembolism are observed.

The M-protein assay used to determine response may be impaired by elotuzumab interference.

A risk for atypical infections exists.

Proposed action

The Delegate considers that elotuzumab is appropriate for inclusion on the ARTG, based upon the data presented at dossier submission, providing the sponsor satisfactorily addresses the remaining comments regarding the product information below. The indication being:

> *Empliciti (elotuzumab) is indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.*

Conditions of registration

As per the biochemistry summary of submission, the following conditions are mandated:

Batch Release Testing & Compliance with Certified Product Details (CPD)

- § It is a condition of registration that all batches of Empliciti (elotuzumab) 300/400 mg Lyophilised powder for IV infusion, vial imported into Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
- § It is a condition of registration that each batch of Empliciti (elotuzumab) 300/400 mg Lyophilised powder for IV infusion, vial imported into Australia is not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch.

The sponsor must supply:

- · Certificates of Analysis of all active ingredient (drug substance) and final product.
- · Information on the number of doses to be released in Australia with accompanying expiry dates for the product and diluents (if included).

- Evidence of the maintenance of registered storage conditions during transport to Australia.
- Five (5) vials of each batch for testing by the TGA Laboratories Branch together with any necessary standards, impurities and active pharmaceutical ingredients (with their Certificates of Analysis) required for method development and validation.

Request for ACPM advice

- What does the committee consider the appropriate population in whom there is a positive risk-benefit for the use elotuzumab?
- Should the PI & CMI document a potential risk of atypical infection given the observed adverse event profile?
- The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

Summary

Despite recent improvements in response rates with the advent of immunomodulatory group of drugs (IMiDs), MM remains an incurable disease with the continued need for new, novel therapies and combination approaches. Elotuzumab is a novel humanised IgG1 mAb targeted against SLAMF7, a glycoprotein expressed on myeloma and NK cells.

Elotuzumab offers a unique mechanism of action as a new therapeutic monoclonal antibody through its dual effect of mediating antibody dependent cell cytotoxicity (ADCC) and directly stimulating NK cells. Elotuzumab demonstrated compelling evidence of benefit as measured by clinically meaningful improvements in PFS, response rate, durability of response, and early trend in OS. Based on the intent to treat (ITT) definition of PFS as assessed by the independent review committee (IRC), there was a 32% reduction in the risk of progression. The hazard ratio (HR) of E-Ld to Ld was 0.68 (97.61% CI: 0.55, 0.85; P-value = 0.0001).

Elotuzumab has an acceptable and manageable safety profile in relapsed or refractory MM subjects and there were minimal incremental AEs reported beyond those associated with lenalidomide. Overall, elotuzumab in combination lenalidomide and dexamethasone has a favourable benefit/risk profile.

BMS welcomes the recommendation from the TGA Delegate that Empliciti (elotuzumab) is appropriate for inclusion on the ARTG. The sponsor has accepted the conclusion from the clinical evaluator that there was insufficient data provided to support the clinical efficacy of the combination of elotuzumab with bortezomib and dexamethasone, or in combination with thalidomide and dexamethasone to provide an assessment of benefit-risk. The sponsor also agrees with the TGA Delegate that limiting the indication statement to use in patients who have received one to three prior therapies may deny patients who have received more than three prior therapies obtaining a clinical benefit for patients who suffer multiple relapses.

In line with the recommendation from the TGA Delegate, BMS has therefore revised the proposed indication statement as follows:

> *Empliciti (elotuzumab) is indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.*

Elotuzumab has also now been approved for the treatment of multiple myeloma in the US (30 November 2015), EU (11 May 2016), Canada (21 June 2016) and Switzerland (6 June 2016).

Questions raised by TGA Delegate

- *What does the committee consider the appropriate population in whom there is a positive risk-benefit for the use elotuzumab?*

Unmet medical need

MM is a source of significant morbidity and mortality in Australia. Estimates for 2015 indicate that approximately 1730 people will be diagnosed with MM and 965 deaths will be attributable to the disease. Overall, MM accounts for 1% of all malignant tumours and 10% to 15% of haematopoietic neoplasms.

The therapeutic landscape of MM has changed markedly in the past decade with the introduction of the IMiDs (thalidomide, lenalidomide) and the first-in-class proteasome inhibitor bortezomib). These new approaches to therapy have produced significantly higher response rates and improved intervals of both PFS and overall survival, yet MM remains an incurable disease. The 5 year relative survival at diagnosis in Australia between the years 2007-2011 was 44.8%. Consequently, there remains the need for new, novel therapies and combination approaches. Elotuzumab is a novel humanised IgG1 mAb targeted against SLAMF7, a glycoprotein expressed on myeloma and NK cells. Elotuzumab exerts a dual effect by mediating ADCC and directly stimulating NK cells. Thus, elotuzumab offers a unique mechanism of action as a new therapeutic monoclonal antibody for the treatment of patients with MM.

Efficacy

The efficacy data included in the submission to support the elotuzumab combination regimen with lenalidomide and low dose dexamethasone (hereafter referred to as the E-Ld regimen) is based upon the results from CA204004, a Phase III, randomised, controlled study and supported by data from HuLuc63- 1703, a Phase Ib/II, dose escalation study providing longer term experience with elotuzumab.

Elotuzumab demonstrated compelling evidence of benefit as measured by clinically meaningful improvements in PFS, response rate, durability of response, and early trend in OS.

The CA204004 trial demonstrates elotuzumab 10 mg/kg combined with standard of care therapy (E-Ld) in relapsed and refractory disease results in a clinically meaningful median PFS of 18.5 months compared to significantly shorter PFS with lenalidomide and low-dose dexamethasone treatment (the Ld regimen) of 14.3 months. More importantly, a higher proportion of subjects experienced a prolonged benefit as evidenced by a 1 and 2-year PFS rate of 68% and 39%, respectively for E-Ld compared with 56% and 26%, respectively, for the Ld group. Based on the ITT definition of PFS as assessed by the IRC, there was a 32% reduction in the risk of progression. The HR of E-Ld to Ld was 0.68 (97.61% CI: 0.55, 0.85; P-value = 0.0001).

The IRC-assessed objective response rate (ORR), based on European Group for Blood and Bone Marrow Transplant (EBMT) criteria, was 78.5% (95% CI: 73.6, 82.9) for E-Ld versus 65.5% (95% CI: 60.1, 70.7) for Ld (common odds ratio E-Ld/Ld: 1.94 (99.5% CI: 1.36, 2.77; P-value= 0.0002; adjusted alpha level of significance: 0.005). Furthermore, the improvement in objective response rate (ORR) is bolstered by the median durability of response of 20.7 months for E-Ld versus 16.6 months for Ld.

Finally from the immature OS data which was included in the original dossier submitted for evaluation, the preliminary trend in OS favouring elotuzumab treatment was consistently observed with 1 and 2 year OS rates of 91% and 74% with E-Ld, respectively,

compared with 83% and 68% for Ld. Although the data are immature from at this stage of the trial, OS favours the E-Ld treatment arm with a hazard ratio of 0.71 (95% CI 0.54, 0.93).

Safety

Elotuzumab has an acceptable and manageable safety profile in relapsed or refractory MM subjects when combined with Ld. Minimal incremental adverse events (AEs) were reported beyond those associated with lenalidomide therapy, particularly evidenced by exposure adjusted event rates. Infusion reactions are mitigated with a standard premedication regimen and infusions of 10 mg/kg of elotuzumab up to 5 mL/min appear safe and tolerable. The safety profile of elotuzumab supports its use in long-term treatment, adults <65 years and elderly patient populations and in those with normal or impaired renal function. The clinical evaluator commented that the safety profile of elotuzumab combination therapy is similar to that of thalidomide or bortezomib alone.

Benefit-risk assessment

Elotuzumab's immunotherapeutic effect induces effective and long-lasting clinical outcomes and represents an important approach to treating MM. Overall, the addition of elotuzumab to Ld demonstrated similar safety to Ld alone. The overall safety profile of elotuzumab compares favourably with several other currently approved agents used in the relapsed/refractory MM setting.

As acknowledged by the TGA Delegate, the use of currently available therapies such as bortezomib, thalidomide and lenalidomide can sometimes be limited by the occurrence of peripheral neuropathy and risk of thromboembolism. However, elotuzumab has not demonstrated any meaningful incremental toxicity when used in combination.

As noted by the TGA Delegate, efficacy of elotuzumab was also demonstrated among a number of high risk subgroups which have been associated with poorer outcomes, for example, cytogenetic categories (presence or absence of (4:14), t(14:16) or del17p), baseline B2 microglobulin concentration and degree of renal impairment.

The sponsor has accepted the conclusion from the clinical evaluator that there was insufficient data provided to support the clinical efficacy of the combination of elotuzumab with bortezomib and dexamethasone, or in combination with thalidomide and dexamethasone to provide an assessment of benefit-risk. The sponsor also agrees with the TGA Delegate that limiting the indication statement to use in patients who have received one to three prior therapies may deny patients who have received more than three prior therapies obtaining a clinical benefit for patients who suffer multiple relapses.

The sponsor believes that the use of elotuzumab in combination with lenalidomide and dexamethasone in patients who have received at least one prior therapy is an appropriate population where a positive benefit-risk assessment has been clearly demonstrated. BMS agrees with the TGA Delegate that the following proposed indication would be appropriate:

> *Empliciti (elotuzumab) is indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.*

- *Should the PI & CMI document a potential risk of atypical infection given the observed adverse event profile?*

Myeloma patients have a 7 fold increased risk of bacterial infections and 10-fold increased risk of viral infections compared to those without myeloma. Infections are a frequent cause of hospitalisations for patients with myeloma. Treatment with antibiotics, antivirals or antifungal agents is common in the course of managing myeloma.

It is widely known that patients with myeloma commonly experience infections due to the underlying disease and concomitant corticosteroid use. This is well understood by physicians in Australia. Patients are provided with education on this topic, such as the Myeloma Foundation Australia Patient Guide.

BMS proposes to update the Precautions section of the PI with the following text:

> *Infections, including severe and life-threatening opportunistic infections, were observed more often among patients that were treated with elotuzumab, in combination with lenalidomide and dexamethasone than in patients that were treated with lenalidomide and dexamethasone alone in a clinical trial in patients with multiple myeloma that received at least 1 prior therapy. The most commonly encountered infections that occurred more often in patients treated with elotuzumab were nasopharyngitis, upper respiratory tract infection, pneumonia and herpes zoster. Patients should be monitored for signs of infection and treated promptly.*

Although the sponsor accepts that risk of infection should be described in the PI, the sponsor does not agree that it should be necessary to recommend prophylaxis against atypical infection.

The CA204004 study did not mandate anti-infective prophylaxis. To address the question whether prophylactic treatment may meaningfully decrease susceptibility to infections, antiviral and antibacterial prophylaxis concomitant medications for each subject in study CA204004 were analysed by flagging subjects who started antibacterial or antiviral therapy on or before the treatment start date, and which were ongoing at the time of the first infection or until end of treatment.

Table 8 shows the subjects who had any grade infection and Grade 3-4 infection. Additionally, the time to first infection and duration of infection are presented by arm for patients with and without prophylactic therapy.

Table 8: Infection summary by prophylactic antibacterial/antiviral treatment: all treated subjects with infection.

	Number of Subjects (%)			
	Prophylactic Treatment		No Prophylactic Treatment	
	E-Ld	Ld	E-Ld	Ld
	N=100	N=111	N=218	N=206
Infections and Infestations				
Any Grade	77 (77.0)	81 (73.0)	182 (83.5)	155 (75.2)
Grade 3-4	23 (23.0)	20 (18.0)	66 (30.3)	57 (27.7)
Time to first infection of any grade (months)				
Median	2.43	2.53	2.30	2.69
Duration of first infection of any grade (days)				
Median	13.0	14.0	13.0	12.0

Table 8 shows a lower frequency of infection for subjects with prophylactic therapy than those without prophylactic therapy in both treatment arms. However, the differences were too small to mandate prophylactic treatment. No difference is seen in the median time to first infection or the median duration of infection, across all arms, regardless of the presence of prophylaxis or treatment arm. Since this was not a pre-planned analysis, a bias in selection of patients who were treated with prophylactic treatment may lessen the validity of such an analysis.

Other issues raised by TGA Delegate

Hepatotoxicity

The sponsor does not consider the addition of hepatotoxicity to the Precautions section of the PI to be necessary. Across the majority of patients with abnormal liver function tests there were plausible explanations for the change in liver function and the longer exposure period in the E-Ld group compared with the Ld-group also confounds interpretation. However, since TGA has not accepted these previously submitted views from the sponsor, BMS reluctantly proposes to add the following wording into the PI:

> *Elevations in liver enzymes (aspartate transaminase/alanine transaminase [AST/ALT] greater than 3 times the upper limit, total bilirubin greater than 2 times the upper limit, and alkaline phosphatase less than 2 times the upper limit) consistent with hepatotoxicity were reported in 2.5% and 0.6% of E-Ldand Ld-treated patients in a clinical trial of patients with multiple myeloma (N = 635). Two patients experiencing hepatotoxicity were not able to continue treatment; however, 6 out of 8 patients had resolution and were able to continue treatment. In 7 out of the 8 patients, there were confounding risk factors such as concurrent steatic hepatitis, cholelithiasis or infection.*
>
> *Monitor liver enzymes periodically. Stop Empliciti upon Grade 3 or higher elevation of liver enzymes. After return to baseline values, continuation of treatment may be considered.*

Inclusion of OS data in PI

The sponsor agrees to remove the overall survival data from the PI which was added as part of the Section 31 response.

Based on the OS data which was included in the original dossier submitted to, and evaluated by, the TGA, the sponsor proposes to instead include the following statement in the Clinical Trials section of the PI:

> *The 1- and 2-year rates of OS for Empliciti in combination with lenalidomide and dexamethasone treatment were 91% and 73%, respectively, compared with 83% and 69%, respectively, for lenalidomide and dexamethasone treatment.*

Interference of elotuzumab with detection and monitoring of M-protein

BMS agrees to move the text on the interaction of elotuzumab to the Precautions section. BMS would like to propose an additional sentence for inclusion as indicated below:

> *Empliciti is a humanized IgG kappa monoclonal antibody that can be detected on both the serum protein electrophoresis (SPEP) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein. This interference can impact the determination of complete response and possibly relapse from complete response in patients with IgG kappa myeloma protein.* ***Therefore, the M-protein assay should not be used in isolation in the clinical assessment of response in patients with IgG kappa disease.***

Conditions of registration

The sponsor acknowledges the implementation of EU-RMP version 1.1 dated 10 December 2015 with ASA version 1 dated 29 July 2015, and any future updates as agreed by the TGA, as a condition of registration. The sponsor also acknowledges the mandatory requirements for batch release testing and compliance with the Certified Product Details as conditions of registration.

Conclusion

Despite recent improvements in response rates with the advent of IMiDs, MM remains an incurable disease with the continued need for new, novel therapies and combination approaches. Elotuzumab offers a unique mechanism of action as a new therapeutic monoclonal antibody for the treatment of patients with MM. Elotuzumab has demonstrated clinically meaningful benefits in combination with lenalidomide and dexamethasone in treating MM patients who have received at least one prior therapy. Importantly, efficacy was also demonstrated among a number of high risk subgroups which are associated with poorer outcomes. Furthermore, elotuzumab has an acceptable and manageable safety profile in relapsed or refractory MM subjects when combined with Ld. Overall, elotuzumab in combination lenalidomide and dexamethasone has a favourable benefit-risk profile with a unique mechanism of action compared with current standard of care therapies. BMS welcomes the TGA Delegate's recommendation to include Empliciti (elotuzumab) on the ARTG.

Advisory Committee considerations

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Empliciti lyophilised powder for IV infusion, vial containing 300 mg and 400 mg of elotuzumab to have an overall positive benefit-risk profile for the Delegate's amended indication**;**

> *Empliciti is indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.*

In making this recommendation, the ACPM:

- Noted that currently there are several options for relapsed, refractory disease but ultimately patients will run out of treatment options either due to loss of response or toxicity.
- Noted that there is insufficient efficacy to warrant registration of elotuzumab in combination with bortezomib and dexamethasone.
- Noted that AEs include infusion reactions, neutropenia, infections, second primary malignancies, peripheral neuropathy, hepatotoxicity and thromboembolism.
- Noted that a small proportion of patients had viral infections (particularly zoster and herpes simplex) antiviral prophylaxis should be considered on a case by case basis in accordance with local hospital policies.
- Noted that lymphopenia was a common side effect, and would recommend PJP prophylaxis be considered by the treating specialist on a case by case basis.
- Noted that M-protein assay used to determine response may be impaired by elotuzumab interference.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration and advised on the inclusion of the following:

- Batch Release Testing and Compliance with Certified Product Details (CPD)

Proposed PI/CMI amendments

The ACPM agreed with the Delegate to the proposed amendments to the PI and CMI. The PI should list all recorded infections (particularly those that were more common in the elotuzumab group than the comparator group), and note neutropenic sepsis as a complication.

Specific advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

- *What does the committee consider the appropriate population in whom there is a positive risk-benefit for the use elotuzumab?*

The ACPM agreed that elotuzumab has positive risk-benefit when used in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.

- *Should the PI & CMI document a potential risk of atypical infection given the observed adverse event profile?*

The ACPM accepted the current revised PI wording for the risk of infection. The ACPM also agreed that there is no indication for routine prophylaxis in all cases.

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Empliciti (elotuzumab) 300 mg and 400 mg lyophilised powder for IV infusion for the following indications:

> *Empliciti (elotuzumab) is indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.*

Specific conditions of registration applying to these goods

- It is a condition of registration that all batches of Empliciti (elotuzumab) 300/400mg Lyophilized powder for intravenous (IV) infusion, vial imported into Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
- It is a condition of registration that each batch of Empliciti (elotuzumab) 300/400mg Lyophilized powder for IV infusion, vial imported into Australia is not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch.

  The sponsor must supply:

  - Certificates of Analysis of all active ingredient (drug substance) and final product.
  - Information on the number of doses to be released in Australia with accompanying expiry dates for the product and diluents (if included).
  - Evidence of the maintenance of registered storage conditions during transport to Australia.
  - Five (5) vials of each batch for testing by the TGA Laboratories Branch together with any necessary standards, impurities and active pharmaceutical ingredients (with their Certificates of Analysis) required for method development and validation.

Attachment 1. Product Information

The PI approved for Empliciti at the time this AusPAR was published is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

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