28 January 2016
EMA/129497/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Empliciti

International non-proprietary name: elotuzumab

Procedure No. EMEA/H/C/003967/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADA	anti-drug antibody
ADCC	antibody-dependent cellular cytotoxicity
AST	aspartate aminotransferase
AUC	area under the serum concentration-time curve
Bd	bortezomib+dexamethasone
BE	bioequivalence
CI	confidence interval
Cmax	maximum concentration
Cmin	minimum concentration
CavgSS	average concentration at steady state
CL	Clearance
CR	Complete response
CrCl	creatinine clearance
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
E-Ld	elotuzumab+lenalidomide+dexamethasone
ER	exposure-response
ESRD	end-stage renal disease
HR	hazard ratio
IA	interim analysis
Ig	immunoglobulin
IMiD	immunomodulatory drugs
IR	infusion reaction
IRC	independent review committee
ISS	International Staging System
IV	intravenous
Ld	lenalidomide+dexamethasone
KM	Kaplan-Meier
LDH	lactate dehydrogenase
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MM	multiple myeloma
MTD	maximum tolerated dose
mAbs	monoclonal antibodies

NAb	neutralizing antibodies
NK	natural killer (cells)
NRF	Normal renal function
ORR	objective response rate
OS	overall survival
PD	pharmacodynamics
PFS	progression free survival
PK	pharmacokinetics
PO	per os (orally)
PPK	population pharmacokinetics
PR	Partial response
PY	patient-years
Q2W	every 2 weeks
QD	Once daily
SAE	serious adverse event
RI	renal impairment
RO	receptor occupancy
RR	relapsed/refractory
SCT	stem cell transplant
SLAMF7	Signaling Lymphocyte Activation Molecule Family 7
SOC	system organ class
SPM	second primary malignancy
SQ	subcutaneous
SRI	severe renal impairment
TTP	time to progression
TTR	time to objective response

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Bristol-Myers Squibb Pharma EEIG submitted on 3 July 2015 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Empliciti, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 20 February 2014.

Empliciti was designated as an orphan medicinal product EU/3/12/1037 on 09 August 2012. Empliciti was designated as an orphan medicinal product in the following indication: treatment of multiple myeloma.

The applicant applied for the following indication: combination therapy for the treatment of multiple myeloma in adult patients who have received one or more prior therapies.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Empliciti as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency's website: ema.europa.eu/Find medicine/Rare disease designations.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that elotuzumab was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision CW/1/2011 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

New active Substance status

The applicant requested the active substance elotuzumab contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 18 November 2010, 15 November 2012, 21 March 2013 and 20 March 2014. The Scientific Advice pertained to quality and clinical aspects of the dossier.

Licensing status

A new application was filed in the following countries at the time of submission of the application: US.

The product was not licensed in any country at the time of submission of the application.

Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Pieter de Graeff Co-Rapporteur: Daniela Melchiorri

- The application was received by the EMA on 3 July 2015.
- Accelerated Assessment procedure was agreed-upon by CHMP on 25 June 2015.
- The procedure started on 23 July 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 12 October 2015. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 12 October 2015. In accordance with Article 6(3) of Regulation (EC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days.
- The PRAC Rapporteur Risk Management Plan (RMP) Assessment Report was adopted by PRAC on 6 November 2015.
- During the meeting on 19 November 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 19 November 2015.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 21 December 2015.
- The PRAC Rapporteur Assessment Report on the applicant's responses to the List of Questions was circulated on 6 January 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 13 January 2016.
- The Rapporteurs circulated the updated Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 21 January 2016.
- During the meeting on 28 January 2016, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Empliciti. On the same day, the CHMP adopted a report on similarity of Empliciti with Thalidomide Celgene, Revlimid, Imnovid, Farydak and Kyprolis.

2. Scientific discussion

2.1. Introduction

Multiple myeloma (MM) is a haematological malignancy resulting from the uncontrolled proliferation of monoclonal plasma cells, which leads to production of monoclonal immunoglobulin (known as M-protein) with substantial immunosuppression and end-organ damage. MM is an incurable disease and accounts for 10% of all haematological malignancies. The incidence in Europe is 4.5-6/100.000/year with a median age at diagnosis between 65 and 70 years. The mortality is 4.1/100.000/year. Almost all patients with MM

evolve from an asymptomatic premalignant stage termed monoclonal gammopathy of undetermined significance (MGUS). In some patients, an intermediate asymptomatic but more advanced pre-malignant stage termed smouldering (or indolent) MM can be recognised.

The course of MM is highly variable, and the clinical behaviour is heterogeneous. Prognostic factors that have been identified to be capable of predicting this heterogeneity in survival are: serum ß2-microglobulin, albumin, C-reactive protein and lactate dehydrogenase. The International Staging System (ISS) relies on the combination of the level of serum ß2-microglobulin and albumin in 3 different stages. ISS 3 is associated with the poorest outcome.

Cytogenetics is also a major prognostic factor. The two genetic abnormalities t(4;14) and deletion(17p) are mostly associated with a poorer outcome. Chromosome 1 abnormalities and t(14;16) are also adverse prognostic factors.

Although therapy has improved in the last decade, most patients with MM will ultimately relapse. After the introduction of chemotherapy, prognosis improved with a median survival of 24 to 30 months and a 10-year survival rate of 3%. Although second and later remissions can be achieved with further therapy, myeloma typically reappears more aggressively after each relapse, leading to decreased duration of response and culminating in treatment-refractory disease with short survival times. With the introduction of newer therapies in recent times, median survival has been reported to improve further to 45 to 60 months from the diagnosis of the disease (National Cancer Institute 2013).

Treatment should be initiated in patients with active myeloma fulfilling the CRAB criteria, i.e. hyperCalcaemia (>11.0 mg/dl), Renal failure (creatinine >2.0 mg/ml), Anaemia (Hb <10 g/dl), and active Bone lesions). Other indications for treatment include symptomatic hyperviscosity, recurrent bacterial infections, and amyloidosis with organ involvement (McCarthy, Hahn, Hematology, 2013).

First line treatment options contain at least one of the novel therapies, i.e. proteasome inhibitors and/or immunostimulatory drugs, followed by autologous stem cell transplantation (ASCT), if indicated. Depth of response after autologous transplantation appears to correlate with the duration of disease control before disease progression occurs with the need for salvage therapy. In Europe, bortezomib, thalidomide (as first line treatment) and lenalidomide are approved in combination regimens for the treatment of multiple myeloma.

Relapsed and/or refractory patients typically receive salvage therapy (if possible, this could include a (2nd) autologous or allogeneic hematopoietic stem cell transplantation) until relapse or toxicity and then go onto the next salvage option. In this setting, bortezomib- and lenalidomide-based regimens are the most commonly used in combination with corticosteroids, to which sometimes also an alkylator or an anthracycline is added. Despite improvement in PFS and OS for patients with early relapsed MM with these agents, 40-60% of patients do not respond to therapy and nearly all relapse after one of these regimens. In this setting, for patients who have received at least 2 prior therapies, including bortezomib and an IMiD, and have shown relapsed or refractory disease, pomalidomide (in combination with dexamethasone) and panobinostat (in combination with bortezomib and dexamethasone) are approved agents in the EU. The proteasome inhibitor carfilzomib in combination with lenalidomide and dexamethasone was approved in the EU for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.

Elotuzumab is an immunostimulatory humanised, IgG1 monoclonal antibody that specifically targets the human SLAMF7 (signaling lymphocyte activation molecule family member 7) protein. SLAMF7 is highly expressed on multiple myeloma cells independent of cytogenetic abnormalities. SLAMF7 is also expressed on natural killer cells, normal plasma cells, and other immune cells including some T cell subsets,

monocytes, B cells, and pDCs (plasmacytoid dendritic cells), but is not detected on normal solid tissues or haematopoietic stem cells (SmPC, section 5.1).

Elotuzumab directly activates natural killer cells through both the SLAMF7 pathway and Fc receptors enhancing anti-myeloma activity in vitro. Elotuzumab also targets SLAMF7 on myeloma cells and facilitates the interaction with natural killer cells to mediate the killing of myeloma cells through antibody-dependent cellular cytotoxicity (ADCC). In nonclinical xenograft models, elotuzumab has demonstrated synergistic activity when combined with lenalidomide or bortezomib (SmPC, section 5.1).

The applicant requested the approval for the following indication: Empliciti is indicated as combination therapy for the treatment of multiple myeloma in adult patients who have received one or more prior therapies (see sections 4.2 and 5.1).

The final indication following CHMP review of this application 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 (see sections 4.2 and 5.1).

The recommended dose of Empliciti is 10 mg/kg administered intravenously 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. Treatment should continue until disease progression or unacceptable toxicity (SmPC, section 4.2).

2.2. Quality aspects

2.2.1. Introduction

Elotuzumab is a humanised IgG_1 monoclonal antibody, produced in a NS0 mouse myeloma-based cell line. It targets Signaling Lymphocytic Activation Molecule Family 7 (SLAMF7, also known as CS1), a cell surface glycoprotein.

Empliciti is presented as powder for concentrate for solution for infusion consisting of elotuzumab (300 mg and 400 mg strengths) formulated with a citrate buffer, sucrose and polysorbate 80. The product is presented in a Type I glass vial and is administered after reconstitution with water for injections followed by dilution with either sodium chloride 0.9% or 5% glucose injection. After reconstitution, each mL of concentrate contains 25 mg elotuzumab.

2.2.2. Active Substance

General Information

Elotuzumab consists of the complementarity-determining regions (CDRs) of the mouse antibody, MuLuc63, grafted onto human IgG_1 heavy and kappa light chain framework regions.

The elotuzumab molecule consists of two identical heavy chain subunits and two identical light chain subunits. Based on the primary sequence, the intramolecular disulfide linkages of the heavy chain are between cysteine residues 22 and 96, 146 and 202, 263 and 323, and 369 and 427. The intramolecular disulfide linkages of the light chain are between cysteine residues 23 and 88, and 134 and 194. The heavy chain and light chain subunits have a disulfide linkage between heavy chain cysteine residue 222 and light chain cysteine residue 214. The two heavy chain subunits have one disulfide linkage between cysteine residue 228 of each chain and another disulfide linkage between cysteine residue 231 of each chain. Elotuzumab has a consensus site for N-linked glycosylation at asparagine residue 299 of the heavy chain. Elotuzumab glycans consist predominantly of complex, core-fucosylated, biantennary structures.

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

The predominant molecular isoform has a heavy chain without C-terminal lysine and with the G0F/G0F glycoform.

The relative molecular mass of the predominant molecular isoform of elotuzumab (calculated mass) is 148.1 kDa (Light chain: 23.4 kDa; Heavy chain: 50.6 kDa).

Manufacture, characterisation and process controls

Bristol-Myers Squibb, 6000 Thomson Road, East Syracuse, New York 13057, USA is responsible for manufacturing of the active substance.

Cell banking

A two-tiered cell banking system of MCB and WCB was established. Up to now an MCB, two WCBs and an end-of-production cell bank (EPCB) have been prepared. Acceptable characterisation results of MCB, WCB and end-of-production cell bank were provided. Cell bank testing is performed in accordance with current ICH guidelines and sufficient information was provided. A protocol for qualification of future WCBs was included in the CTD.

Viral testing of MCB, WCB and EPCB revealed Type A and Type C retrovirus-like particles detectable by transmission electron microscopy (TEM). In addition, testing of the EPCB with three virus assays showed evidence of the presence of xenotropic, amphotropic or mink cell focus (MCF) retrovirus. In accordance with ICH Q5A, the Applicant provided results of three unpurified (pre-harvest) and three purified bulk (unformulated active substance) lots tested for retrovirus. The pre-harvest lots tested positive for retrovirus-like particles, however all three purified lots tested negative.

Manufacture

The upstream steps of the elotuzumab manufacturing process are initiated with the thaw of a WCB vial. The culture is expanded in a series of shake flasks and a cell bag. A seed bioreactoris inoculated with the cell bag bioreactor content which is subsequently expanded. The bioreactor is harvested based on culture duration and cell viability, to ensure consistency for downstream processing. Each bioreactor inoculation is a closed operation.

The primary recovery steps remove cells and cell debris from the production bioreactor contents and contribute to the viral inactivation (VI) capacity of the process. Following the neutralisation step a detergent VI step is performed to inactivate potential adventitious and endogenous viral agents.

The detergent-treated viral-inactivated clarified bulk (VI-CB) is transferred to purification for downstream processing.

The VI-CB is processed across a series of chromatography columns. The resulting product pool from the final chromatography step is processed through a viral filter to remove potential endogenous and/or adventitious viral agents.

The virus-filtered (VF) product pool is concentrated and buffer exchanged to generate the unformulated active substance (UDS). The UDS is diluted to a final protein concentration and formulated with a polysorbate 80 solution and filtered into bioprocess containers to make the formulated active substance (FDS).

The FDS in bioprocess containers is stored refrigerated until it can be frozen using a liquid nitrogen blast freezer for long-term frozen storage. The FDS is shipped frozen to the finished product manufacturing facility.

Process evaluation/validation

The manufacturing process has been adequately established based on small-scale studies, full scale manufacturing lots, and ongoing process verification. The approach, including decision criteria, have been clearly described.

Impurity clearance studies at small scale and manufacturing scale showed clearance of process and product-related impurities.

Satisfactory process qualification data were submitted for manufacturing scale lots.

Sufficient validation data were provided regarding sanitisation of columns and filters.

Manufacturing process development

The current process is labelled Process D. It differs from process C1 mainly with regard to addition of a detergent viral inactivation step at the end of the upstream process and two reprocessing steps at the end of the downstream process. Material from four subsequent processes has been used in two comparability exercises: process B and C material was compared to Process C1 material, and Process C1 material to Process D material. Process B and C material was manufactured in a different facility than the process C1 and D material (current facility). In addition, there are scale other differences between the different processes. Clinical studies relevant for the current marketing authorisation application have used predominantly Process C and C1 material. Analytical comparability was shown for active substance manufactured with the four different processes.

Extensive manufacturing process development data were provided, including a number of multivariate studies (Design of Experiments (DoE) studies, response surface models (RSM)). Origin of in-process controls (IPCs) from these and other studies is sufficiently explained. In general the multivariate studies did not detect significant risks to the Critical Quality Attributes (CQAs), probably due to pre-existing knowledge with regard to optimal manufacturing conditions. Sufficient information was provided regarding the use of DoE and to justify proposed critical IPCs based on a conventional assessment approach.

Control System

Proposed critical IPCs are clearly reviewed and justified by data presented in the developmental and other studies.

Characterisation

Active substance from the process performance qualification campaign was used in the characterisation studies. Data were provided regarding physicochemical properties, primary structure, secondary structure, higher order structure, biological activity, and post-translational modifications.

The primary structure of elotuzumab is consistent with that predicted by the cDNA. Variants in primary structure were detected on both the heavy and light chains. Higher order structural characterisation indicates the presence of low levels of HMW and trace level of low-molecular weight (LMW).

The structural modifications that affect the overall charge profile of elotuzumab have been adequately characterised. Correlations between biological activity and specific charge variants were established by

analysis of variants isolated. Results demonstrated an understanding of species that have reduced or increased activity.

The predominant glycosylation forms have been identified and characterised.. Two glycans account for the majority of glycoforms present within elotuzumab. Minor glycoform species were suitably identified.

Sufficient characterisation data were provided to substantiate an understanding of the species that have decreased biological activities.

Forced degradation studies revealed the major degradation pathways for elotuzumab.

Reference standards

Three different research reference standards were used during development and the current primary reference standard (PRS) and working reference standard (WRS) have been described. Preparation, storage conditions, acceptance criteria for qualification of PRS and WRS are described and comparative testing results of all reference standards are reported. Stability testing is also described. Criteria for qualification of future reference standards have been provided.

Container Closure system

Container closure integrity testing studies were provided, with satisfactory results.
Extractables/leachables studies identified no extractables or leachables at levels which could represent a hazard to the patient.

Specification

The release and shelf life specification for elotuzumab active substance is considered acceptable.

It is noted that most analytical methods and associated quantitative limits also apply to the finished product.

The Applicant submitted extensive method descriptions, which are fairly complete and allow independent assessment. The proposed analytical methods were supported by adequate validation data.

In general, the Applicant proposes a fairly straightforward set of tests, which is commonly accepted for monoclonal antibodies. Deletion of tests for potential process-related impurities (which were performed during development) was sufficiently justified.

Justifications for the proposed specification were provided and are based on a sufficient number of batches. A statistical approach (tolerance intervals) was used to define the acceptable ranges.

Stability

Registration stability studies were conducted on three batches of elotuzumab active substance in accordance with ICH stability guidance, and were aimed to demonstrate that the active substance is stable up to 36 months when stored at the recommended condition of <-35°C (-40°C ±5°C). All batches were made at the intended commercial manufacturing facility, at the intended commercial manufacturing scale, and are representative of the quality of material used in clinical and non-clinical studies. These three batches were manufactured according to the commercial manufacturing process . In addition, stability studies have been conducted on supportive batches of elotuzumab active substance, demonstrating the stability of the active substance at -40°C. Samples were stored in containers representative of the commercial storage bioprocess containers, and were assessed by the acceptance criteria in the proposed active substance specification.

In the real time methods no detectable degradation occurs, which is not surprising in view of the frozen storage condition. At accelerated and stressed conditions, minor changes could be discerned.

Accelerated (5°C) stability studies were conducted through 6 months. Under the stress storage condition at 25°C/40%RH or 25°C/60%RH, similar but greater changes were observed, consistent with what is expected for a therapeutic protein. Room temperature/room light studies showed elotuzumab is susceptible to degradation from exposure to ambient light, and should be protected from light.

2.2.3. Finished Medicinal Product

The Applicant presented a summary of the quality characteristics for elotuzumab for injection that were considered to guide the commercial formulation and process development work.

Empliciti is presented as powder for concentrate for solution for infusion consisting of elotuzumab formulated with a citrate buffer, sucrose and polysorbate 80. The product is presented in a Type I glass vial and is administered after reconstitution with water for injections followed by dilution with either sodium chloride 0.9% or 5% glucose injection. After reconstitution, each mL of concentrate contains 25 mg elotuzumab. Two strengths of lyophilised finished product, 400 mg/vial and 300 mg/vial, have been developed for commercialisation. The pack size for each strength is one vial.

The entire Empliciti infusion should be administered with an infusion set and a sterile, non-pyrogenic, low-protein-binding filter (with a pore size of 0.2-1.2 µm) using an automated infusion pump.

The container closure system was chosen based on protection, compatibility, safety, and performance to ensure the quality of the finished product throughout its shelf life. Elotuzumab for injection, 300 mg and 400 mg presentations, are packaged in a 20-cc Type I flint glass vial, stoppered with a 20-mm film-coated butyl lyophilisation rubber stopper, and sealed with a 20-mm aluminum crimp seal with Flip-Off button. In addition to the primary package, the commercial packaging system for both presentations includes a paperboard folding carton.

Evolution of the finished product formulation during development was adequately described in the dossier. The 300 and 400 mg presentations are identical.

The Applicant studied compatibility of elotuzumab/Empliciti with a number of common infusion materials (including in-line filters). In the same study design, stability after reconstitution/dilution was studied.

Manufacture of the product and process controls

Bristol-Myers Squibb S.r.l., Loc. Fontana del Ceraso, Frosinone, 03012, Anagni, Italy is the manufacturer responsible for EU batch release.

The manufacturing process for elotuzumab for injection includes conventional steps for aseptic filling, lyophilisation and stoppering and has been deemed acceptable.

The commercial manufacturing process was adequately validated.

Product specification

The release and shelf life specification for the finished product have been deemed acceptable. The only difference between the 300 mg and 400 strength presentations is the fill volume, so the acceptance criteria differ only for the “Drug Content” method.

Non-compendial methods for use in release and/or stability testing of elotuzumab finished product are the same as those for the active substance; reference is made to the active substance section for description

and validation of these methods. The omission of tests has been adequately justified for parameters that will not change due to formulation-fill-freeze-drying.

Furthermore, appropriate pharmaceutical tests were included (e.g. particulate matter; water content). The choice of tests is deemed sufficiently justified.

The limits/acceptance criteria of the tests are compendial or otherwise sufficiently justified.

Stability of the product

The shelf life for the finished product (unopened vial) is 3 years at 2-8°C protected from light.

Appropriate batches from the commercial process were included in the stability studies, and this is deemed acceptable.

Although the amount of available data for the 300 mg/vial presentation is limited, it is agreed that the shelf life for the 400 mg/vial can be extrapolated to the 300 mg/vial, based on the identical formulation and strength, and based on the accelerated data.

In addition, data from photostability and freeze-thaw studies were provided and do not give rise to specific comments or concerns.

Chemical and physical in-use stability of the reconstituted and diluted solution has been demonstrated for 24 hours at 2-8°C and protected from light.

From a microbiological point of view, the solution for infusion should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C protected from light. The reconstituted or diluted solution should not be frozen. The solution for infusion may be stored for a maximum of 8 hours of the total 24 hours at 20-25°C and room light. This 8 hour period should be inclusive of the product administration period.

Adventitious agents

The elotuzumab active substance manufacturing process includes measures to prevent introduction of potential adventitious agents:

- Procedures and controls for the sourcing and quality of cell culture and purification raw materials;
- Testing of cell banks (MCB, WCB, EPCB) for sterility, mycoplasma, MVM, and endogenous and potential adventitious viral agents;
- Testing for bioburden, endotoxin, Mycoplasma, and *in vitro* adventitious viral agents of the pre-harvest samples from each production batch;
- Inclusion of orthogonal viral clearance steps in the manufacturing process.
- In order to minimise the risk of BSE/TSE, no raw materials of animal origin are used in the Elotuzumab manufacturing process, which includes all steps and processing beginning from the designated master cell bank.

Retroviral like particles (type A and C) were detected in three batches of unprocessed (pre-harvest) bulk. Three batches of purified bulk material (unformulated active substance) were shown to test negative for retroviruses, in accordance with ICH Q5A.

Four orthogonal steps of the Elotuzumab manufacturing process were evaluated for their ability to remove or inactivate model viruses:

- Viral inactivation by detergent;

- Viral inactivation by low pH;

- Anion exchange (AEX) chromatography;

- Viral filtration;

The viral clearance studies were performed using a panel of model viruses with a wide range of physicochemical characteristics. In response to questions, full study reports were provided, confirming these conclusions.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

No major issue was identified during the procedure. Some of the concerns addressed by the Applicant are described below.

Active substance

A summary of the WCB manufacturing process and characterisation tests for qualification of future WCBs is provided. However, no protocol with description of manufacture and testing acceptance criteria for replacement of WCB was initially provided. In response to a question, a protocol for qualification of future WCBs was included.

In response to a question about conflicting results from a reverse transcriptase (RT) assay in relation to C-type retroviruses, the Applicant committed to evaluate alternate assays that may provide greater specificity and/or to provide additional data to support continued use of the fluorescent PCR-based RT (F-PBRT) assay. The Applicant is recommended to provide an update on the outcome of this evaluation once additional data and information are available.

Proposed critical in-process controls (IPCs) for the active substance are clearly reviewed and justified by data present in the developmental and other studies. However, the control strategy initially proposed was not considered acceptable, since the relevance and the purpose of multivariate design of experiments (DoE) studies was not fully clear, and since ranges studied in the DoEs were narrow. Therefore, the robustness of these steps could not be assessed and sufficient control of the downstream process was therefore not substantiated.

In addition, for two CQAs no critical IPCs or active substance release limits have been defined. It was proposed to upgrade non-critical IPCs for these CQAs to critical IPCs.

The Applicant was asked to address several points regarding qualification of scale-down models, management of DoE studies and process parameter criticality definition. Sufficient information was provided to resolve uncertainties regarding the use of DoE and to justify proposed critical IPCs based on a conventional assessment approach. Questions about the control system were sufficiently addressed by including a number of additional critical IPCs.

For a potential process-related impurities eluting from two chromatography resins, insufficient data was provided to substantiate how safe levels are guaranteed. In their responses, the Applicant provided adequate data to address these issues. The Applicant is recommended to implement a new IPC for this process-related impurity.

The Applicant was asked to provide sanitisation validation for columns and filters. This issue was sufficiently resolved by data provided in response to this question in combination with sanitisation data presented in vendor studies and viral sanitisation data presented in the viral clearance studies.

The facility design and operating procedures in place are adequate for the control of bioburden and endotoxin in the active substance was considered justified. Nevertheless, it is recommended that at the first future routine GMP inspection, control of bioburden is specifically inspected.

Criteria for qualification of future reference standards were provided.

In general, the Applicant submitted extensive method descriptions, which are fairly complete and allow independent assessment. A number of deficiencies were identified in relation to the method descriptions, system suitability criteria, validations, and the associated specification limits. These issues were appropriately addressed.

The stability studies and data sufficiently support the claimed shelf life of 36 months at ≤ -35°C, and protected from light.

The cell-based potency assay was not performed for all time points in accelerated and stressed stability studies and for the final time points (24 to 36 months) for the long-term stability study. The Applicant is recommended to put under long-term stability the first three commercial batches of the active substance. The initial time point should correspond to the release time, and all the assays should be performed according the stability plan and in compliance to the frequency of testing indicated by the ICH Q1A-R2 guideline. Since the same approach was also adopted for the finished product, the same commitment applies for the finished product long-term stability study. Any out-of-specification should be reported to the competent Authority.

Finished product

In relation to the manufacturing process of the finished product, an appropriate overview of the defined critical steps, intermediates, CPPs, IPCs, and hold times was given. Appropriate justification was provided based on the manufacturing process development.

The Applicant studied compatibility of elotuzumab/Empliciti with a number of common infusion materials (including in-line filters). In the same study design, stability after reconstitution/dilution was studied. Although the study suffered from limitations due to the bracketing/matrixing design which tries to address several real-life factors concomitantly, the Applicant further explained the approach and justified that although the order of conditions in the study is different compared to the SmPC advice, all conditions have been studied. Therefore, the provided data and additional justification sufficiently support the SmPC claim. It was considered that there was little gain in requesting additional studies.

In relation to the use of an in-line filter for administration of the product, the Applicant explained that although there is no compelling product quality consideration requiring the mandatory use of an in-line filter at the point of patient administration, the use of an in-line filter should be stated in the SmPC for the following reasons:

- All clinical administration of elotuzumab infusions have been conducted using an in-line filter at the point of patient administration;

- To mitigate the potential risk of patient exposure from extraneous particles and fibers that may be introduced during handling and infusion preparation with the lyophile, an in-line filter with a pore size of 0.2 µm to 1.2 µm should be used.

The Applicant's justification that the use of an in-line filter for administration of the product is necessary was accepted.

Adventitious agents safety

The Applicant was asked to provide the full reports of the virus clearance studies summarised in module 3.2.A.2.2 in order to allow an independent assessment. The studies were provided, allowing full assessment of viral safety issues.

According to ICH Q5A absence of detectable virus should be confirmed in at least 3 lots of purified bulk. In response to questions, the Applicant provided viral testing results of three batches of unprocessed (pre-harvest) bulk and of three batches of purified bulk material (unformulated active substance). No detectable virus was found in the purified bulk lots.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Overall, the quality of Empliciti is considered to be in line with the quality of other approved monoclonal antibodies. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The fermentation and purification of the active substance are adequately described, controlled and validated. The active substance is well characterised with regard to its physicochemical and biological characteristics, using state-of-the-art methods, and appropriate specifications are set. The manufacturing process of the finished product has been satisfactorily described and validated. The quality of the finished product is controlled by adequate test methods and specifications.

Viral safety and the safety concerning other adventitious agents including TSE have been sufficiently assured.

The overall Quality of Empliciti is considered acceptable when used in accordance with the conditions defined in the SmPC. However, several quality Recommendations on Quality aspects, have been made.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommended several points for investigation.

2.3. Non-clinical aspects

2.3.1. Introduction

Due to the lack of species-specific cross-reactivity, no relevant animal species or valid transgenic mouse models were identified in which to conduct the nonclinical toxicology studies. Given this limitation, the nonclinical safety program consisted primarily of *in vitro* safety studies utilizing human cells and tissues (a study of haemolytic potential in human blood, and a human tissue cross-reactivity study with a comprehensive panel of human tissues) and limited *in vivo* animal studies (including a local tolerance study in rabbits in compliance with GLP regulations).

2.3.2. Pharmacology

Primary pharmacodynamic studies

Elotuzumab (HuLuc63) is a humanized IgG1 monoclonal antibody specific for human SLAMF7, a signalling molecule abundantly expressed on the surface of multiple myeloma (MM) cells. The ability of Elotuzumab to bind SLAMF7 was assessed in comparison with the originator mouse monoclonal antibody Luc63 by plasmon resonance (Study Report RTR5). Both antibodies were immobilized on chips and challenged by BIAcore to analyse the binding with solutions containing two different dimeric forms of human SLAMF7-Fc at concentrations ranging from 0.25 to 512 nM. The originator and humanized antibody showed a very

similar binding profile with a Kd of 42.4 and 43.7 nM for the murine and human antibody, respectively, using as binding moiety the chimeric form with human Fc and 28.5 nM and 28.9 nM using that with mouse Fc.

The binding of HuLuc63 and MuLuc63 to peripheral blood leukocyte subsets was assessed by flow cytometry (Study Report RTR8). The humanized antibody, assessed at saturating concentration of 10µg/mL, bound almost all NK and NKT cells and a high percentage of $CD8^+$ T cells. A smaller and variable percentage of $CD4^+$ T lymphocytes and $CD14^+$ monocytes was also recognized whereas binding to B lymphocytes ($CD20^+$/HLA DR^+) and granulocytes was negligible.

Evaluation of HuLuc63 binding to peripheral blood and bone marrow cells from 7 MM patients by flow cytometry showed that the antibody stained most of plasma cells, NK, NKT and $CD8^+$T cells and at a lower extent $CD4^+$ T cells. The antibody did not bind to hematopoietic stem cells ($CD34^+$) obtained by cytoapheresis in 3 MM and 7 lymphoma patients with the exception of one lymphoma patient who had been repeatedly stimulated with G-CSF due to resistance to peripheralization of stem cells (Study Report RTR9).

A cross-reactivity study with nonhuman primate whole blood was conducted to evaluate the binding of elotuzumab to various leukocytes in blood samples from healthy chimpanzees and cynomolgus and rhesus monkeys (Study RTR21). Elotuzumab exhibited no binding to NK, NKT, CD8+ T cells, or monocytes in blood samples from chimpanzees, rhesus, or cynomolgus monkeys; no binding to CD4+ T cells from chimpanzees was observed (binding to CD4+ T cells was not conducted in rhesus or cynomolgus monkeys). Binding of elotuzumab to B cells was detected in blood samples from cynomolgus and rhesus monkeys, but not from chimpanzee. The observed binding of elotuzumab to cynomolgus and rhesus monkey B cells was highly variable between animals and was likely nonspecific, as elotuzumab does not bind directly to recombinant SLAMF7 from either of these species when expressed in heterologous cell transfectants.

A cross-reactivity study with recombinant SLAMF7 protein was conducted to determine the cross-reactivity of elotuzumab for nonhuman primate SLAMF7 including chimpanzee, cynomolgus, and rhesus monkey (Study RTR18). The study results indicated that elotuzumab specifically bound only to human SLAMF7 and did not recognize recombinant SLAMF7 from any of the nonhuman primate species evaluated, as assessed by binding either to purified Fc fusion proteins in an ELISA or to full-length SLAMF7 on the surface of living cells (e.g. transfected cell lines) using flow cytometry.

The binding of the originator murine antibody MuLuc63 was evaluated by immunohistochemistry (Study Report RTR10) using normal human tissues (heart, liver, lung, kidney, colon, duodenum, ileum, stomach, lymph node, spleen, tonsil, cerebrum, cerebellum, spinal cord, trigeminal ganglion, dorsal root ganglion, vagus nerve, aorta, adrenal, thyroid, pituitary, pancreas, parathyroid, cervix, ovary, uterus, mammary gland, testes, prostate, ureter, bladder and urethra). In most cases the antibody stained leukocytes that were also positive for CD138, a plasma cell marker. In some organs such as liver and nervous ganglia a positive staining for CD138-negative leukocytes was observed. Binding to plasmacytoma cells was showed by immunohistochemistry with the same murine antibody in tissue sample of MM patients (Study Report RTR11). A cross-reactivity study in human and nonhuman tissues was conducted using immunohistochemistry (IHC) (Study RTR12). The nonhuman species that were evaluated included the cynomolgus and rhesus monkeys, mini-pig, dog, rabbit, rat, and mouse. Overall, no elotuzumab staining was detected in any of the nonhuman tissues tested (mainly spleen, tonsil, colon and brain). These data indicated the lack of cross-species reactivity of elotuzumab for nonhuman species and that none of the species examined were relevant for toxicology evaluation. Elotuzumab-specific cell-surface staining was observed in the mononuclear cells of human tonsil, spleen, lymph node, colon and trigeminal ganglion. No staining was detected in the human cerebrum, cerebellum, spinal cord, or the dorsal root ganglion.

Efficacy in inducing an antibody-dependent cellular cytotoxicity (ADCC) was assessed by measuring the release of LDH in co-cultures of L-363 cells, the human plasma-cell line positive for SLAM7 used as the target, with peripheral mononuclear cells (PBMC) obtained from either 11 healthy donors or 23 multiple myeloma patients in the presence of HuLuc63 at concentrations ranging from 1 ng/mL to 10 µg/mL (Study Report RTR16). In all the samples a dose-dependent increase of LDH-release was observed with HuLuc63 as compared to a control antibody. Healthy and myeloma subjects did not significantly differ when the effects were compared to a single concentration (1 µg/mL). No correlation was found between magnitude of cytotoxicity and the frequency of NK cells in the sample.

Similarly HuLuc63 mediated ADCC in a ^{51}chromium release assay performed using L363 and OPM2 plasmacytoma cells as targets and healthy donor PBMC as effectors (Study Report RTR13). SLAM7-negative epithelial cell lines, were not sensitive to by HuLuc63 and PBMC exposure until transfection with human SLAM7, thus showing the specificity of antibody-mediated killing. Depleting PBMC of B, T lymphocytes or monocytes did not reduce antibody-mediated cytotoxicity, whereas depletion of NK cells significantly reduced either ADCC or antibody-independent cellular cytotoxicity. No complement-mediated cytotoxicity was observed up to 100 µg/mL.

After comparison of two anti-SLAM7 mouse antibodies for *in vivo* anti-tumour activity against neoplastic plasma cells, MuLuc63 was selected for further development being significantly more potent than b MuLuc90 in a subcutaneous xenograft model in immunodeficient mice inoculated with L363 cells when administered by i.p. at 10 mg/kg thrice a week for three weeks, with 5 out of 8 animals showing no tumour at the end of the experiment. Different doses with the same schedule, 1 mg/kg, 5 mg/kg and 10 mg/kg of MuLuc63 were tested in the same model and whereas the highest dose induced tumour eradication in 8 out of 9 mice the other two doses were less effective with 5 and 1 out of 9 animals free of tumour at the end of the experiment with 5 and 1 mg/kg, respectively. Similar results were obtained when OPM2 cells were used to induce subcutaneous tumours, however in this case the lower dose (5 mg/kg) caused regression of the tumour in all the animals, whereas 10 mg/kg in 6 out of 9. The efficacy of the humanized antibody was also compared with the originator antibody *in vivo* in the two animal models precedently used. The antibodies were administered i.p. at 10 mg/kg twice a week for 7 doses. Data obtained from the L363 model revealed that MuLuc63 was significantly more potent than HuLuc63 in reducing tumour growth, whereas in the OPM2 model both antibodies showed similar efficacy in terms of tumour growth in responding mice, even if MuLuc63 eradicated the tumour in 8 out of 9 animals and HuLuc63 in 5 out of nine.

Higher doses of HuLuc63, 15 and 20 mg/kg, did not increase efficacy in the L363 model. Since these antibodies showed a similar affinity for the ligand, the different potency has been attributed to the difference in the Fc portion which is murine IgG2a for MuLuc63 and human IgG1 for HuLuc63 (Study Report RTR14).

A PK/PD study using the OPM2 model assessed the effect of increasing doses (0.1, 0.5, 1.5 and 10 mg/kg) of HuLuc63 i.p. administered every 3 days for a total of 7 administrations(Study Report RTR15).Serum levels of the antibody were assessed by a validated ELISA assay. A dose-dependent inhibition of tumour growth was observed, with the exception of 0.1 mg/kg dose. Antibody serum levels revealed no antitumor effect with concentration below 2 µg/mL, whereas the highest dose showed antibody serum concentration in the range 70-430 µg/mL.

HuLuc63 was also tested in combination with other anti-tumour agents. Using the OPM2 model, HuLuc63 at a suboptimal dose (1 mg/kg twice a week for 5 weeks) in combination with bortezomib, a proteosome inhibitor widely used in the treatment of MM, showed to be more efficacious as compared to HuLuc63 and bortezomib used alone (Study Report RTR26).

In addition, using the same model, HuLuc63 at 0.5 mg/kg dose given twice a week for 7 administrations, enhanced the effect of pomalidomide at 5 mg/kg, a dose inducing about 60% inhibition of tumour growth in single treatment. Elotuzumab in combination with both pomalidomide and dexamethasone increased the efficacy compared to single treatments. In addition, the combination of elotuzumab with pomalidomide and dexamethasone (5 mg/kg) showed a greater efficacy as compared to the single use or the combination of elotuzumab and pomalidomide or dexamethasone (Study Report IO00047).

Study DP-5348 evaluated the effect of elotuzumab in combination with lilirumab, an anti-human natural killer cell inhibitory receptors KIR2DL monoclonal antibody, in a MM xenograft model induced in immunodeficient RAG-1KO mice transgenic for human KIR2DL3. OPM-2 cells were injected subcutaneously in matrigel, starting from 10 days after cell injection, when the tumour reached about 50 mm^3 elotuzumab was administered by i.p. at 0.5 mg/kg or 2 mg/kg twice a week for 7 administrations. The highest dose induced a decrease of tumour volume in 7 out of 9 mice whereas the lower in 3 out of 8. Also survival of the mice was increased compared to controls. In combination with lilirumab (i.v. at day 11 and 24), the frequency of response increased to 7 out of 10 and also survival was prolonged supporting the involvement of NK cells, conserved in RAG-1KO mice, however in an experiment with NK cell depletion the antitumour effect of elotuzuamb was only partially reduced. When the treatment was started later (day 17 from cell inoculation) tumour growth was only reduced, with a higher efficacy when used in combination with lilirumab; consistently also survival was prolonged.

The antitumour activity in the OPM2 model of HuLuc63 given as a single administration at a dose from about 0.5 to 5 mg/kg was enhanced by the combination with an anti-mouse CD137 activating antibody, which is able to increase NK-mediated ADCC and is not active *per se* in this model. In particular doses of about 0.5 and 5 mg/kg induced complete regression of the tumour in 7 out of 8 and 6 out of 8 mice, respectively (Study Report OPM-2).

Secondary pharmacodynamic studies

No secondary pharmacodynamic studies were submitted (see discussion on non-clinical aspects).

Safety pharmacology programme

No safety pharmacology studies were submitted (see discussion on non-clinical aspects).

Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were submitted (see discussion on non-clinical aspects).

2.3.3. Pharmacokinetics

To support the pharmacokinetic and toxicokinetic studies, ELISA methods were used to quantify elotuzumab in SCID mouse and rhesus monkey serum (non-GLP studies). Serum ELISA methods for both matrices were developed at PDL Biopharma, Inc (Fremont, California). A validated ELISA method was used for the analysis of SCID mouse serum, while a qualified ELISA method was used to analyze rhesus monkey serum. The results for the standard curve (well fitted to the regression model) and the analytical QCs indicated that the assay methods were precise and accurate for the analysis of elotuzumab in these studies. Analysis for ADA was not performed for these studies.

The pharmacokinetics of elotuzumab was studied following repeat-dose IP administration in an OPM2 xenograft mouse model as part of a dose-ranging study to examine the relationship between circulating drug concentrations and biological activity (study TR06011). Following IP administration once every 3 days for a total of 7 doses, a dose-response relationship was shown as average serum concentrations of elotuzumab increased as dose increased from 0.1 to 10 mg/kg. Maximal anti-tumor activity was reached at mean elotuzumab serum concentrations of 70 to 430 μg/mL (low to high concentration range at the

10-mg/kg dose) and minimal biological activity was seen at 2 to 13 μg/mL (low to high concentration range at the 0.5-mg/kg dose).

In study RTR15 mice bearing OPM2 tumors were randomized to different treatment groups when their tumors reached an average size of 83 mm^3 (range: 45–146 mm^3); the treatment groups consisted of treatment with HuLuc63 at doses of 0.1, 0.5, 1, 5, and 10 mg/kg. The control group received isotype control antibody (HuPr1_SB1161_98071) at 10 mg/kg. Dosing was once every 3 days for a total of 7 doses. Blood was collected at 8 hours after the first dose (C1 max), immediately before the second dose (C1 min), immediately before the 7th dose (C6 min), 8 hours after the last dose (C7 max), and one dose-interval after the last dose (terminal bleed).

2.3.4. Toxicology

Single dose toxicity

An exploratory single-dose IV infusion toxicokinetic and tolerability study of elotuzumab was conducted to evaluate potential off-target toxicity in rhesus monkeys (Study TR07150) for a period of 45 days.

Table 1 Single dose toxicity studies with elotuzumab

Study ID (GLP)	Species/ Sex/Number/ Group	Dose/Route	Approx. lethal dose / observed max non-lethal dose	Major findings
TR07150/930046731; Report and Amendment 1 (NON GLP)* 2007	1/sex/dose Monkeys (rhesus) 4-6 years old weighting 4.2-6.8 kg M, 3.9-5.4 kg F	0, 30, 100 i.v. 30 min infusion Animals were sacrificed and necropsied on Day 45.	> 100 mg/kg (AUC $_{0\text{-inf}}$ 335 to 447 hr.mg/mL).	No evidence of treatment-related toxicity up to the higher dose used

In this study, elotuzumab was administered via continuous IV infusion over 30 minutes to 3 groups of rhesus monkeys (1 monkey/sex/group) at doses of 0, 30, or 100 mg/kg. Single IV administration of elotuzumab at dose levels of 30 or 100 mg/kg (≤ AUC[INF] range of 335 to 447 mg•h/mL) were well tolerated. All monkeys survived to scheduled sacrifice. There were no elotuzumab-related effects on clinical observations, body weight, food consumption, clinical pathology, immunophenotyping, organ weights, or macroscopic and microscopic evaluations. Systemic exposure (AUC and Cmax) to elotuzumab increased in an approximately dose-proportional manner, with no sex-related differences. The high dose of 100 mg/kg corresponds to exposures of approximately 8× above that observed in humans at the recommended dose of 10 mg/kg (AUC[INF] of 49,482 μg•h/mL after the first dose).

Repeat dose toxicity

No repeat dose toxicity studies were submitted (see discussion on non-clinical aspects).

Genotoxicity

No genotoxicity toxicity studies were submitted (see discussion on non-clinical aspects).

Carcinogenicity

No carcinogenicity toxicity studies were submitted (see discussion on non-clinical aspects).

Reproduction Toxicity

No reproductive toxicity studies were submitted (see discussion on non-clinical aspects).

Toxicokinetic data

Toxicokinetic parameters were analysed in an exploratory nonGLP single-dose study in rhesus monkeys (Study TR07150 described under single toxicology section). Following a single IV dose in rhesus monkeys, the increase in systemic exposure to elotuzumab was dose proportional between 30 and 100 mg/kg, and was similar in males and females. The area under the serum concentration-time curve extrapolated to infinity [AUC(INF)] was 118 and 194 mg•h/mL at 30 mg/kg, and 335 and 447 mg•h/mL at 100 mg/kg. The initial volume of distribution after a single dose of elotuzumab in rhesus monkeys was low (46.3 to 61.5 mL/kg). Also, consistent with the slow clearance of antibodies, total serum clearance ranged from 0.155 to 0.299 mL/h/kg and the apparent elimination half-life (T-HALF) was 8 to 14.8 days. Analysis for ADA was not performed.

Local Tolerance

The local tolerance of elotuzumab was assessed in a single-dose IV study in rabbits (Study TR06050). Elotuzumab was administered at 5 mg/mL into the right marginal ear vein, with an injection rate of 1 mL/minute. No irritation or local tolerance issues were observed at this concentration and injection rate that were comparable to those recommended for human use (maximum concentration of 6.6 mg/mL and infusion rate $\leq$ 2 mL/minute). Additionally, there were no unscheduled deaths and all animals appeared clinically normal at all observation periods. Evaluation of body weight and food consumption, and macroscopic and microscopic assessments did not reveal any elotuzumab-related effects.

Other toxicity studies

A methods qualification study using normal human tissues, chimpanzee and rhesus monkey tissues was conducted to qualify assay conditions for tissue cross-reactivity studies with elotuzumab (Study TR06052). A precomplexing method was shown to be specific, sensitive, and reproducible for immunohistochemical staining with HuLuc63 in human cross-reactivity studies. Appropriate positive and negative control tissues were identified. Two concentrations (10 and 3 μg/mL) of elotuzumab were selected for staining in a subsequent human tissue crossreactivity study with a comprehensive panel of human tissues.

A definitive cross-reactivity study of elotuzumab with normal human tissues was conducted to evaluate a comprehensive panel of approximately 36 tissues from 3 different donors for elotuzumab reactivity (Study TR06051). Elotuzumab showed reactivity with cell membranes and/or cytoplasm of variable numbers of plasma cells and/or immunoblasts (B-lineage cells in the process of differentiating into plasma cells) in multiple tissues including bone marrow, breast, gastrointestinal tract (colon [large intestine], esophagus, small intestine, stomach), liver, lymph node, fallopian tube (oviduct), pancreas, salivary gland, spleen, thymus, thyroid, tonsil, ureter, uterus (body [endometrium], cervix). Staining of the plasma cells and immunoblasts was expected as the epitope (SLAMF7) recognized by elotuzumab is expressed on these cells. There was no specific cross-reactivity with any other tissue element in any of the human tissues examined.

2.3.5. Ecotoxicity / environmental risk assessment

No ERA was submitted (see discussion on non-clinical aspects).

2.3.6. Discussion on non-clinical aspects

The primary pharmacodynamics of elotuzumab has been extensively studied. The mode of action of elotuzumab specifically related to its capacity of binding to SLAMF7, and the physiological diversity of the effects of SLAMF7 governs the diversity of the pharmacodynamic effects of elotuzumab. Elotuzumab was

developed as a humanized mAb (IgG1) that targets SLAMF7, a cell surface glycoprotein for which expression is restricted to malignant myeloma cells and subsets of normal leukocytes in humans (NK cells, NKT cells, a subset of CD8+ T cells, and plasma cells). The primary mechanism of action of elotuzumab is NK-mediated ADCC of Malignant Myeloma cells. Elotuzumab mediated ADCC was both NK cell- and CD16-dependent. SLAMF7 is also a regulator of NK cell function. Binding of elotuzumab to SLAMF7 on NK cells directly activates these immune cells and enhances their anti-myeloma activity *in vitro*. Elotuzumab is inhibitory to lymphocytes because of other downstream molecules i.e. SHIP-1 and the protein phosphatase receptor CD45.

Lack of SLAMF7 in cells prevented to observe any effect of elotuzumab, which is an important observation in respect to species selection for safety testing.

The antitumour activity of elotuzumab has been clearly shown *in vitro* and in *vivo*. *In vivo* elotuzumab induced eradication of tumours in a number of mice, indicating its usefulness in this respect. Remarkably that this is true for mouse studies with human xenografts, indicating that the SLAMF7-mediated stimulation of NK-cell activity (not possible with mouse NK-cells) is not essential for the full activity of elotuzumab.

No secondary pharmacodynamic and pharmacodynamic drug interaction studies were conducted due to the absence of adequate animal models. SLAMF7 is a protein important for cell-cell interaction in the lymphoid system.

Binding to SLAMF7 by elotuzumab is therefore not expected to have effects on CNS parameters or cardiovascular functioning. The absence of specific safety pharmacology studies is therefore acceptable.

A repeat-dose range-finding study in OPM2 tumor-bearing SCID mice receiving elotuzumab once every 3 days for a total of 7 doses showed that, in general, mean serum elotuzumab concentrations increased with repeated dosing, indicating accumulation of elotuzumab over the dosing period. In addition, average serum concentrations of elotuzumab increased as dose increased from 0.1 mg/kg to 10 mg/kg. The relationship between circulating drug concentrations and biological activity of elotuzumab in the OPM2 xenograft mouse model suggests that maximal anti-tumor activity is reached at mean elotuzumab serum concentrations of 70 to 430 μg/mL (range of serum concentrations at the 10-mg/kg dose) and minimal biological activity is seen at 2 to 13 μg/mL (range of serum concentrations at the 0.5-mg/kg dose). The applicant gives high weight to this study, and applies this range of serum concentrations also to the human situation. From another study in mice, however, it is clear that the Fc-binding and ADCC properties cannot be translated quantitatively to the human situation.

A series of comparative species qualification (binding) studies was conducted to support species selection for toxicology studies. Interestingly, although the amino acid sequence of the SLAMF7 protein is highly conserved among primate species (human sequence is 98%, 90%, and 89% identical to that of chimpanzee, cynomolgus, and rhesus monkey, respectively), the comprehensive binding analyses revealed that elotuzumab does not bind SLAMF7 of nonhuman primates, or other nonclinical species including mouse, rat, rabbit, mini-pig, and dog. The applicant has tried to overcome the lack of an animal species by making a transgenic mouse with SLAMF7. Therefore transgenic mice expressing human SLAMF7 were generated to explore an alternative approach for the nonclinical safety evaluation of elotuzumab. However, the mouse characterization results indicated that the human SLAMF7 transgenic mouse was not a valid alternative animal model for toxicology testing due to a lack of human SLAMF7 expression in both resting and activated T cells in this mouse model as compared to humans.

As in clinical practice elotuzumab will be given in addition to small molecules such as immunomodulatory drugs or proteasome inhibitors, combination studies was an important contribution in the primary

pharmacodynamics. With respect to bortezomib and lenalidomide, a synergy with elotuzumab has been shown.

Despite the knowledge that rhesus monkeys are not a responsive animal species, the applicant has conducted a pharmacokinetic study in rhesus monkeys. Following an IV infusion in these monkeys, the single-dose toxicokinetic was characterized by a low initial volume of distribution and clearance and a long T-1/2. Increases in systemic exposure to elotuzumab in rhesus monkeys were dose proportional between 30 and 100 mg/kg, and exposure was similar between males and females. Although these results have a potential value for the interpretation of this toxicity study, they are not relevant for humans.

ADAs were not analyzed in either the mouse study or the monkey study, as it was not deemed pertinent to the interpretation of the results.

In accordance with relevant guideline (Guidance for Industry, S6(R1): Addendum to preclinical safety evaluation of biotechnology-derived pharmaceuticals) no metabolism, tissue distribution, or excretion studies with elotuzumab have been conducted in animals. The expected *in vivo* degradation of mAbs is to small peptides and amino acids via biochemical pathways that are independent of drug metabolizing enzymes, such as CYP enzymes, so no drug-drug interactions are anticipated.

Elotuzumab only recognizes human SLAMF7 protein. Because elotuzumab does not recognize non-human forms of SLAMF7 protein, in vivo safety data from animal studies are irrelevant. In the same line, no carcinogenicity data are available for elotuzumab in animals, nor were fertility and embryo foetal toxicity studies performed. Non clinical safety information primarily consists of limited in vitro human cell/tissue studies where no safety findings were identified. (SmPC section 5.3).

As elotuzumab is an IgG1 mAb and this subtype is known to be transported across the human placental barrier through interactions with the FcRn receptor, elotuzumab does have the potential for direct fetal exposure, especially at late stages of pregnancy. Although the potential impact of elotuzumab on fetal development has not been evaluated, the lack of notable developmental effects in SLAMF7-deficient mice suggested that inhibition of SLAMF7 via elotuzumab may not result in developmental toxicity.

There is no human experience with elotuzumab during pregnancy. Elotuzumab will be given in combination with lenalidomide, which is contraindicated during pregnancy. No animal data are present regarding the effect on reproductive toxicity because of the lack of an adequate animal model. Empliciti should not be used during pregnancy and in women of childbearing potential, unless the clinical condition of the woman requires treatment with elotuzumab. Women of childbearing potential should use effective contraception (SmPC section 4.6).

Male patients must use effective contraception measures during and for 180 days following treatment if their partner is pregnant or of childbearing potential and not using effective contraception (SmPC section 4.6).

The Summary of Product Characteristics for all medicinal products used in combination with Empliciti must be consulted before starting therapy. When Empliciti is used with lenalidomide there is a risk of foetal harm, including severe life-threatening human birth defects associated with these agents and the need to follow requirements regarding pregnancy avoidance, including testing and contraception. Lenalidomide is present in the blood and sperm of patients receiving the medicine. Refer to the Summary of Product Characteristics for requirements regarding contraception due to presence and transmission in sperm and for additional detail. Patients receiving Empliciti in combination with lenalidomide should adhere to the pregnancy prevention programme of lenalidomide (SmPC section 4.6).

Elotuzumab is not expected to be excreted into human milk. Elotuzumab will be given in combination with lenalidomide and breast feeding should be stopped because of the use of lenalidomide (SmPC section 4.6).

Studies to evaluate the effect of elotuzumab on fertility have not been performed. Thus, the effect of elotuzumab on male and female fertility is unknown (SmPC section 4.6).

An exploratory single-dose IV infusion toxicokinetic and tolerability study of elotuzumab in rhesus monkeys provided evidence that there is no potential off-target toxicity in monkeys. As expected, there were no elotuzumab-related effects in monkeys at IV doses ≤ 100 mg/kg (AUC range of 335 to 447 mg•h/mL), indicating the absence of elotuzumab-related off-target effects.

The data using human tissue indicated that binding of elotuzumab is restricted to expected sites based upon presence of SLAMF7. Elotuzumab showed reactivity with cell membranes and/or cytoplasm of variable numbers of plasma cells and/or immunoblasts in multiple human tissues.

The justification provided by the Applicant for not performing environmental risk assessment studies was considered acceptable since elotuzumab is a protein composed of natural amino acids therefore, unlikely to result in significant risk to the environment. This is in accordance with the “Guideline on Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 corr 21*).

2.3.7. Conclusion on the non-clinical aspects

Elotuzumab has been well characterized in a series of nonclinical pharmacology studies, while pharmacokinetic/toxicokinetic, and toxicologic studies were limited due to the binding properties to the SLAMF7 antigen which is strictly human specific and the non-feasibility of a transgenic animal model expressing this human antigen in T-cells. The relevant information has been included in the SmPC (sections 4.6, 5.1 and 5.3). Clinical trials data were therefore an important source of information to support the safety in patients.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 2 Overview of Study Design Clinical Efficacy Studies

Study/ Phase	Study Population/ Study Design	Number of Subjects	Primary Efficacy Endpoints and Other Efficacy Endpoints	Treatment Regimen	Study Status
Elotuzumab / Lenalidomide / Dexamethasone (E-Ld)					
CA204004 (Phase 3)	Relapsed and/or refractory MM after 1 to 3 prior therapies with documented progression from immediately prior MM therapy per EBMT criteria Randomized, controlled, multi-center, open-label.	N=635 treated (318 E-Ld, 317 Ld)	ORR and PFS (co-primary), TTR, DOR (supporting ORR), OS, and PFS/OS rates (EBMT criteria)	Elotuzumab10 mg/kg weekly in C1 & C2, Q2W in C3 and beyond + Ld[a] or Ld alone.	Completed analysis of co-primary / secondary endpoints Subjects remaining in study are on long-term treatment or safety follow-up OS follow-up ongoing
HuLuc63-1703 (Phase 1b/2)	Relapsed or refractory MM after 1 to 3 prior therapies (phase 2 portion) with documented disease progression from immediately prior MM therapy per IMWG criteria. Open-label, multi-center, dose-escalation.	Phase 1b: N=28 treated Phase 2: N=73 treated	ORR TTR, DOR, and PFS (IMWG criteria) MTD (Phase 1b)	Phase 1b: elotuzumab 5, 10, or 20 mg/kg weekly in C1 & C2, Q2W in C3 and beyond + Ld[a] Phase 2: elotuzumab 10 or 20 mg/kg weekly in C1 & C2, Q2W in C3 and beyond + Ld[a]	Completed analysis of primary/secondary endpoints, subjects remaining in study are on long-term treatment or safety follow-up
CA204009 (Phase 2)	Relapsed and/or refractory MM after 1-3 prior therapies with documented progression after or during most recent MM therapy per IMWG criteria Phase 2, randomized, controlled, multi-center, open-label E-Bd vs. Bd	N=150 Treated (75 E-Bd, 75 Bd)	PFS (primary); ORR, TTR, DOR and OS (IMWG criteria)	Elotuzumab 10 mg/kg Days 1, 8, 15 of C1 & C2, Days 1 and 11 of C3-8; and Days 1 and 15 of C9 and beyond + Bd or Bd alone[d]	Completed analysis of primary/secondary endpoints; Subjects remaining in study are on long-term treatment or safety follow-up; OS follow-up ongoing
HuLuc63-1702 (Phase 1)	Previously treated, relapsed or refractory MM after 1–3 prior MM therapies Open-label, multi-center, dose-escalation of elotuzumab given in combination with bortezomib	N=28 Treated	Phase 1: NA -MTD (primary objective); ORR, DOR, TTR, and PFS (EBMT criteria)	Elotuzumab 2.5, 5, 10, or 20 mg/kg following bortezomib administration twice per 21-day cycle. Bortezomib 1.3 mg/m^2 4 times per 21-day cycle Dexamethasone 20 mg po 8 times per 21-day cycle added if	Phase 1: completed

[a] Lenalidomide (Revlimid®) 25 mg po daily on Days 1-21; dexamethasone 40 mg po once weekly on weeks without elotuzumab, and as a split dose of 8 mg IV+28 mg po on weeks with elotuzumab (for Study HuLuc63-1703, this dexamethasone dosing regimen started with Protocol Amendment E).

[d] Bortezomib (Velcade®) 1.3 mg/m^2 administered either IV or SC on Days 1, 4, 8, and 11 of C1-8; and Days 1, 8, and 15 of C9 and beyond. Dexamethasone 20 mg po on Days 1, 2, 4, 5, 8, 9, 11, and 15 of C1 and 2; Days 1, 2, 4, 5, 8, 9, 11, and 12 of C3-8; and Days 1, 2, 8, 9, 15, and 16 of C9 and beyond on days without elotuzumab; and 8 mg IV+8 mg po on days with elotuzumab.

Abbreviations: Bd = bortezomib+dexamethasone; C1/2/3/4/8/9/18/19 = Cycle 1/2/3/4/8/9/18/19; DOR = duration of response; E-Bd = elotuzumab + bortezomib + dexamethasone; E-CTd = elotuzumab + cyclophosphamide + thalidomide + dexamethasone; E-Ld = elotuzumab + lenalidomide + dexamethasone; E-Td = elotuzumab+thalidomide +dexamethasone; EBMT = European Group for Blood and Bone Marrow Transplant; ESRD = end-stage renal disease; IMWG = International Myeloma Working Group; IRC = independent review committee; IV = intravenous(ly); Ld = lenalidomide + dexamethasone; MM = multiple myeloma; MTD = maximum tolerated dose; NA = not applicable; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics; po = per os (orally); Q2W = every 2 weeks; RI = renal impairment; SC = subcutaneous(ly); QD = once daily; SCT = stem-cell transplantation; TTR = time to objective response.

2.4.2. Pharmacokinetics

The pharmacokinetics (PK) of elotuzumab was studied in patients with multiple myeloma (SmPC, section 5.2). Results of pharmacokinetics (PK) of elotuzumab are currently available for 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 (Table 3). Single dose pharmacokinetics of elotuzumab was investigated in 4 studies (HuLuc63-1701, HuLuc63-1702, CA204005 and CA204007) after the administration of the first IV infusion. Multiple-dose pharmacokinetics of elotuzumab was investigated for the dose regimen of every 10 days and every 14 days. The effects of renal impairment on PK of elutuzumab was also investigated (CA204007).

PK data from clinical studies CA204004, CA204005, CA204007, and CA204011 were used for population pharmacokinetics (pop-pk) model. The model was refined with additional PK data from study CA204009.

The pharmacokinetic characteristics of elotuzumab were mainly studied in clinical studies HuLuc63-1701 and HuLuc63-1702 in terms of C_{max}, AUC, V_{ss}, CL and $T_{1/2}$.

Table 3 Summary of clinical studies with pharmacology data of elotuzumab

Study ID/Phase (sponsor)	Design	Treatment	Number of treated subjects	Design of Clinical Pharmacology Related Component of the Study	Contribution to the Clinical Pharmacology Profile
Phase I					
HuLuc63-1701 / Phase I (AbbVie)	Phase 1, multi center, open label, dose escalation study of elotuzumab in subjects with advanced multiple myeloma	Subjects received 4 doses of elotuzumab IV infusion given every other week of 8 week (52/56 day) treatment cycle. Dose cohorts: 0.5, 1, 2.5, 5, 10, and 20 mg/kg	34	PK samples: 0 hour (predose), 30 minutes, 2, 4, 24, 48, 168, and 336 (predose on Day 14) hours post-end of infusion after first and fourth doses on Days 0 and 42; 30 minutes post-end infusion on Day 14; 0 hour (predose) and 30 minutes post-end infusion on Day 28 and retreatment (if applicable); early termination/discontinuation, and at 30-and 60-day follow-ups Biomarker/PD samples: 0 hour (predose), 2, and 4 hours after the first and fourth doses on Days 0 and 42; on Days 2, 7, 14 (predose), 28 (predose) 56, and at 30- and 60-day follow-ups Immunogenicity samples: 0 hour (predose) on Days 0 28, 42, 52/56 and 30- and 60-day follow-ups	PK, biomarkers/ PD, immunogenicity, PPK (sensitivity)
HuLuc63-1702 / Phase I (AbbVie)	A Phase 1/2, multi-center, open-label, dose-escalation study of elotuzumab and bortezomib in subjects with multiple myeloma following one to three prior therapies	Subjects received 4 cycles of IV bortezomib given on Days 1, 4, 8, and 11 and elotuzumab given on Days 1 and 11. Cycles were 21 days long; those with response or stable disease continue for $\geqslant$ 6 treatment cycles or until withdrawal. Subjects with progressive disease at the end of Cycle 2 or Cycle 3 (Day 11) also receive dexamethasone at 20 mg on Days 1, 2, 4, 5, 8, 9, 11, and 12 of each cycle thereafter. Dosing cohorts: Each subject receives 1.3 mg/m2 bortezomib per dose plus elotuzumab at 2.5, 5, 10, or 20 mg/kg. If necessary, dexamethasone was 20 mg/dose.	28	PK samples: 0 hour (predose), 30 minutes, and 2 hours post end of elotuzumab infusion on Day 1, Cycle 1; 0 hour (predose) on Days 4 and 11, Cycle 1; 0 hour (predose) and 2 hours post end of elotuzumab infusion on Day 11, Cycle 1; 0 hour (predose) and 2 hours post end of elotuzumab infusion on Days 1 and 11, Cycle 2; 0 hour (predose) on Day 1 of Cycles 3 and 4; 0 hour (predose) and 2 hours post end of elotuzumab infusion on Day 11, Cycle 3; 0 hour (predose), 30 minutes, and 2 hours post end of elotuzumab infusion on Day 11 of Cycle 4; 0 hour (predose on Day 1 and 0 hour (predose) and 2 hours post end of elotuzumab infusion on Day 11 of continued therapy (all cycles), termination visit, and 30-day follow-up Biomarker/PD samples: screening and at approximate time points similar to PK samples, and at Cycle 4 Day 18 to 21 time point Immunogenicity samples: 0 hour (predose) on Day 1 of Cycle 1, Day 11 of Cycle 3, Day 1 of continued therapy (all cycles), termination visit, and 30-day follow-up	PK, biomarkers/ PD, immunogenicity
HuLuc63-1	Phase	Subjects received	28	PK samples: 0 hour (predose), 30	PK,

703 / Phase I portion (AbbVie)	1b/2, multicenter, open-label, dose escalation study of elotuzumab in combination with lenalidomide and dexamethasone in subjects with relapsed multiple myeloma	elotuzumab IV infusion (Days 1, 8, 15, and 22 of Cycles 1 and 2 and Days 1 and 15 of subsequent cycles), lenalidomide PO (Days 1-21), and dexamethasone (Days 1, 8, 15, and 22 at 8 mg dexamethasone IV and 28 mg dexamethasone PO on dosing days) in 28-day cycles unless discontinued due to disease progression or withdrawal Dosing cohorts: elotuzumab at 5, 10, or 20 mg/kg with 25 mg lenalidomide plus 40 mg dexamethasone		minutes and 2 hours post-end of infusion on Days 1 and 22, 0 hour (predose) and 2 hours post-end of infusion on Day 8, and 0 hour (predose) and 30 minutes post-end of infusion on Day 15 of Cycle 1; 0 hour (predose), and 2 hours post-end of infusion on Days 1and 22 of Cycle 2; 0 hour (predose) and 30 minutes post-end of infusion on Day 1 of Cycle 3 and beyond; Day 28 of last cycle/early termination, and at 30-and 60-day follow-ups Biomarker/PD samples: 0 hour (predose), 30 minutes, and/or 2 hours on Days 1, 8, and 22 of Cycle 1; Days 1 and 22 of Cycle 2; Day 1 of Cycles 3 and 5 and/or beyond; Day 28 of last cycle/early termination; and at 30- and 60-day follow-ups Immunogenicity samples: 0 hour (predose) on Day 1 of each cycle, Day 28 of last cycle/early termination, and 30- and 60-day follow-ups	Biomarkers/ PD, immunogenicity, PPK, E-R analyses
CA204005 / Phase I (BMS)	Phase 1 multiple ascending dose study of elotuzumab in combination with lenalidomide/low-dose dexamethasone in patients with relapsed or refractory multiple myeloma in Japan	Subjects received elotuzumab IV infusion (Days 1, 8, 15, and 22 of Cycles 1 and 2 and Days 1 and 15 of subsequent cycles), Lenalidomide PO (Days 1-21), and dexamethasone (Days 1, 8, 15, and 22) in 28-day cycles unless discontinued due to disease progression or withdrawal Dosing cohorts: elotuzumab at 10 or 20 mg/kg, lenalidomide 25 mg, and dexamethasone (weeks without elotuzumab: 40 mg PO, weeks with elotuzumab: 8 mg IV + 28 mg PO)	6 (3 in each cohort)	PK samples: 0 hour (predose), 30 minutes, and 2 hours post-end of infusion on Days 1 and 22 of Cycle 1 and Day 1 of Cycle 3; 0 hour (predose) and 2 hours post-end of infusion on Day 8 of Cycle 1 and Day 1 of Cycle 2; 0 hour (predose) and 30 minutes post-end of infusion on Day 15 of Cycle 1; 0 hour (predose) on Day 15 of Cycle 1, Day 1 of Cycles 4, 6, and every 3 cycles, end of study/discontinuation; 30- and 60-day follow-ups Immunogenicity samples: 0 hour (predose) on Day 1 of Cycles 1, 2, 3, 4, 6, every 3 cycles, end of study/discontinuation, and 30- and 60-day follow-ups	PK, immunogenicity, PPK
CA204007 / Phase Ib (BMS)	Phase 1b study of elotuzumab in combination with lenalidomide and dexamethasone in subjects with multiple myeloma and normal renal function, severe renal impairmen	Subjects received lenalidomide/ dexamethasone with elotuzumab (10 mg/kg IV infusion on Days 1, 8, 15, and 22 of Cycles 1 and 2 and Days 1 and 15 of subsequent cycles) in 28-day cycles until disease progression, unacceptable toxicity, or the subject meets other criteria for discontinuation of study drug Dosing cohorts: elotuzumab 10 mg/kg, lenalidomide (dose and schedule	26 (NRF, 8; SRI, 9; ESRD, 9)	PK samples after single dose on Day 1 of Cycle 1: 0 hour (predose), end of infusion, 30 minutes, 2, 4, and 24 hours post-end of infusion, immediately prior to and after dialysis on Day 2 or 3, 48, 168, 240, 336, and 504 hours; 0 hour ([predose] 672 hours after dose on Day 1 Cycle 1) on Days 1, 8, 15, and 22 of Cycles 2 and 3; 0 hour (predose) on Day 1 of Cycles 4, 6, 9, 12, 15, 18, end of study/discontinuation; 30- and 60-day follow-ups Immunogenicity samples: 0 hour (predose) on Day 1 of Cycles 1, 2, 3, 4, 6, 9, 12, 15, 18, end of study/discontinuation, and 30- and 60-day follow-ups	Effects of SRI and ESRD on PK, immunogenicity, PPK

	t, or end stage renal disease requiring dialysis	adjusted for renal function), and dexamethasone (weeks without elotuzumab: 40 mg PO, weeks with elotuzumab: 8 mg IV + 28 mg PO)			
Phase II					
HuLuc63-1703 / Phase II portion (AbbVie)	Phase 1b/2, multicenter, open-label, dose-escalation study of elotuzumab in combination with lenalidomide and dexamethasone in subjects with relapsed multiple myeloma	Subjects received elotuzumab IV infusion (Days 1, 8, 15, and 22 of Cycles 1 and 2 and Days 1 and 15 of subsequent cycles), lenalidomide PO QD (Days 1-21), and dexamethasone (weeks without elotuzumab: 40 mg PO, weeks with elotuzumab: 8 mg IV + 28 mg PO).QD (Days 1, 8, 15, and 22 at 8 mg dexamethasone IV and 28 mg dexamethasone PO on elotuzumab dosing days) in 28-day cycles unless discontinued due to disease progression or withdrawal Dosing cohorts: subjects randomized to elotuzumab 10 or 20 mg/kg with 25 mg lenalidomide plus 40 mg dexamethasone	73	PK samples: 0 hour (predose), 30 minutes and 2 hours post-end of infusion on Days 1 and 22, 0 hour (predose) and 2 hours post-end of infusion on Day 8, and 0 hour (predose) and 30 minutes post-end of infusion on Day 15 of Cycle 1; 0 hour (predose), and 2 hours post-end of infusion on Days 1and 22 of Cycle 2; 0 hour (predose) and 30 minutes postend of infusion on Day 1of Cycle 3 and beyond; Day 28 of last cycle/early termination, and at 30-and 60-day follow-ups Biomarker/PD samples: 0 hour (predose), 30 minutes, and/or 2 hours on Days 1, 8, and 22 of Cycle 1; Days 1 and 22 of Cycle 2; Day 1 of Cycles 3 and 5 and/or beyond; Day 28 of last cycle/early termination; and at 30- and 60-day follow-ups Immunogenicity samples: 0 hour (predose) on Day 1 of each cycle, Day 28 of last cycle/early termination, and 30- and 60-day follow-ups	PK, Biomarkers/ PD, PGX, Immunogenicity, PPK, E-R analyses
CA204009 / Phase II (BMS)	Phase 2 study of bortezomib /dexamethasone with or without elotuzumab in subjects with relapsed/refractory multiple myeloma	Subjects were randomized in a 1:1 ratio and received bortezomib/dexamethasone with or without elotuzumab in 21-day cycles for Cycles 1 - 8 and in 28-day cycles beginning with Cycle 9 until disease progression, unacceptable toxicity, or the subject meets other criteria for discontinuation of study drug. Dosing cohorts: Control arm: Bortezomib 1.3 mg/m2 IV or SQ (Days 1, 4, 8, 11 of Cycle 1 to 8 and Days 1, 8, 15 of Cycles 9 and Beyond) and dexamethasone 20 mg PO Investigational arm: elotuzumab 10 mg/kg IV (Days 1, 8, 15 of	Control arm: 75 Investigational arm: 75	PK samples: 0 hour (predose) on Day 1 of Cycles 1 and 2, and end of treatment Biomarker/PD samples: : 0 hour (predose) on Day 1 of Cycles 1 - 18, end of study/discontinuation, and 30- and 60-day follow-ups Immunogenicity samples: 0 hour (predose) on Day 1 of Cycles 1 - 18, end of study/discontinuation, and 30- and 60-day follow-ups	PK, biomarker/PD, PGX, immunogenicity, PPK, E-R analyses

		Cycles 1 and 2, Days 1, 11 of Cycles 3 to 8, and Days 1, 15 of Cycles 9 and Beyond) plus bortezomib (1.3 mg/m2 IV or SQ) and dexamethasone 20 mg PO or 8 mg IV and 8 mg PO			
CA204011 / Phase II (BMS)	Phase 2 biomarker study of elotuzumab monotherapy to assess the association between NK cell status and efficacy in high risk smoldering myeloma	Subjects received elotuzumab IV infusion on Days 1 and 8 of Cycle 1, and Day 1 of Cycle 2 and beyond (Cohort 1) or weekly for 4 weeks in Cycles 1 and 2 and every other week in Cycles 3 and beyond (Cohort 2) Dosing cohorts: elotuzumab 20 mg/kg (Cohort 1) and 10 mg/kg (Cohort 2)	Cohort 1: 15 Cohort 2: 16	PK samples: 0 hour (predose), 30 minutes, and 2 hours post-end of infusion on Day 1 of Cycles 1 and 3; 0 hour (predose) and 2 hours post-end of infusion on Day 8 of Cycle 1; 0 hour (predose) on Day 1 of Cycles 2, 4, 6, 9, 12, 15, and 18; end of study/discontinuation; 30- and 60-day follow-ups Immunogenicity samples: 0 hour (predose) on Day 1 of Cycles 1, 2, 3, 4, 6, 9, 12, 15, 18, and at end of study/discontinuation, and 30- and 60-day follow-ups ECG assessments: : 0 hour (predose), 30 minutes, and 2 hours post-end of infusion on Day 1 of Cycles 1 and 3; 0 hour (predose) and 2 hours post-end of infusion on Day 8 of Cycle 1	PK, biomarker/PD, immunogenicity, PPK, ECG assessments
Phase III					
CA204004 / Phase III (BMS)	Phase 3, randomized, open label trial of lenalidomide/ dexamethasone with or without elotuzumab in relapsed or refractory multiple myeloma	Subjects were randomized 1:1 to receive lenalidomide PO (Days 1-21) /dexamethasone (Days 1, 8, 15, 22) with or without elotuzumab (10 mg/kg IV infusion on Days 1, 8, 15, and 22 of Cycles 1 and 2 and Days 1 and 15 of subsequent cycles) in 28-day cycles until disease progression, unacceptable toxicity, or the subject meets other criteria for discontinuation of study drug. Dosing cohorts: Control arm: lenalidomide 25 mg and dexamethasone 40 mg Investigational arm: elotuzumab 10 mg/kg, lenalidomide 25 mg, and dexamethasone (weeks without elotuzumab: 40 mg PO, weeks with elotuzumab: 8 mg IV + 28 mg PO).	Control arm: 317 Investigational arm: 318	PK samples: 0 hour (predose), 30 minutes, and 2 hours post-end of infusion on Days 1 and 22 of Cycle 1, Day 1 of Cycle 3); 0 hour (predose) and 2 hours post-end of infusion on Day 8 of Cycle 1, Days 1 and 22 of Cycle 2; 0 hour (predose) and 30 minutes post-end of infusion on Day 15 of Cycle 1; 0 hour (predose) on Day 15 of Cycle 3; 0 hour (predose) on Day 1 of Cycles 4, 6, 9, 12, 15, and 18; end of study/ discontinuation; 30- and 60-day follow-ups Immunogenicity samples: 0 hour (predose) on Day 1 of Cycles 1, 2, 3, 4, 6, 9, 12, 15, 18, and at end of study/discontinuation, and 30- and 60- day follow-ups	PK, PGX, immunogenicity, PPK, E-R analyses, ECG assessments

Abbreviations: BMS = Bristol-Myers Squibb; ECG = electrocardiogram; E-R = exposure-response; ESRD = end stage renal disease; IV = intravenous; NRF = normal renal function; PD = pharmacodynamics; PK = pharmacokinetics; PGX

= pharmacogenomics; PO = per os (oral); PPK = population pharmacokinetics; SQ = subcutaneous; SRI = severe renal impairment

Absorption

No bioavailability studies were performed.

Elotuzumab is dosed via intravenous route and therefore is immediately and completely bioavailable (SmPC, section 5.2).

Distribution

The Volume of distribution of elotuzumab has been estimated in MM patients in study HuLuc63-1701, HuLuc63-1702 and study CA204007 with a dose in range of 0.5 mg/kg and 20 mg/kg.

Mean volume of distribution of elotuzumab ranged from 36 mL/kg to 70 mL/kg (2.3-4.6 L for a typical patient) and was independent from the dose in a dose range of 0.5 mg/kg to 20 mg/kg (SmPC, section 5.2).

The metabolic pathway of elotuzumab has not been characterized. As an IgG monoclonal antibody, elotuzumab is expected to be degraded into small peptides and amino acids via catabolic pathways (SmPC, section 5.2).

Elimination

Elimination of elotuzumab was investigated following the first dose (single) in the first cycle of the treatment in study HuLuc63-1701, HuLuc63-1702 and CA204007.

In study HuLuc63-1701, average of total clearance of elotuzumab decreased from 0.80 to 0.22 mL/h/kg with an increase in dose from 0.5 to 20 mg/kg. Terminal elimination half-life ($t_{1/2}$) appeared to increase from 2.1 to 7.8 days along with the increase of dose from 0.5 to 20 mg/kg.

In study HuLuc63-1702, total clearance of elotuzumab decreased from 0.54 to 0.20 mL/h/kg with an increase in dose from 2.5 to 20 mg/kg. Terminal elimination half-life ($t_{1/2}$) appeared to increase from 4.1 to 7.7 days along with the increase of dose from 2.5 to 20 mg/kg.

Terminal half-life in Studies HuLuc63-1701 and HuLuc63-1702 (110 and 140 h [4.6 and 5.8 days], respectively) was shorter than in study CA204007 (204 h [8.5 days]) likely because the PK sampling period was shorter in studies HuLuc63-1701 and -1702, (336 h and 240 h, respectively) compared to study CA204007, where the sampling period was over 672 h.

Following a single dose of 10 mg/kg, the elotuzumab clearance was 13.2 mL/day/kg. Elotuzumab exhibits nonlinear pharmacokinetics with clearance of elotuzumab decreasing from 17.5 to 5.8 mL/day/kg with an increase in dose from 0.5 to 20 mg/kg, suggesting target-mediated clearance, resulting in greater than proportional increases in Area under the Concentration time curve (AUC). Upon discontinuation of elotuzumab in the combination with lenalidomide/dexamethasone, concentrations of elotuzumab will decrease to approximately 3% (approximately 97% washout as estimated by 5 half-lives) of the population predicted steady state maximal serum concentration by 3 months (SmPC, section 5.2).

Dose proportionality and time dependencies

The pharmacokinetics of elotuzumab is nonlinear, due to binding to the target. Dose proportionality was investigated in study HuLuc63-1701 and HuLuc63-1702. In study HuLuc63-1701, following administration of the first dose, C_{max} increased in a dose proportional manner across the dose range of 0.5 to 20 mg/kg. Mean estimates of AUC(TAU) and AUC(INF) increased greater than proportionally with dose over the dose range of 0.5 to 20 mg/kg with estimated slopes of 1.277 (95% confidence interval of 1.159

to 1.399) and 1.328 (95% confidence interval of 1.129 to 1.524), respectively. In study 1702, for both Cycle 1 and Cycle 4, the increase in Cmax and AUC appeared to be more than the increment in dose from 2.5 to 20 mg/kg. . The more than dose-proportional increase in AUC was consistent with the dose-dependent decrease in total clearance (CLT) and increase in T-HALF values in the lower dose range. The decrease in total clearance is expected to be predominantly influenced by the saturation of target-mediated elimination of elotuzumab in lower doses. Under steady-state conditions, elotuzumab clearance was driven by elimination of elotuzumab only from the central compartment. Nevertheless, only dose of 10 mg/kg is proposed for elotuzumab, therefore dose proportionality is not relevant for efficacy and safety.

In study HuLu63-1703 (concomitant with lenalidomide and dexamethasone), PK data was available from 101 subjects (N = 3, 39, and 59 for the 5, 10, and 20 mg/kg dose groups, respectively). Elotuzumab was administered weekly for the first 8 weeks (2 cycles) followed by every two weeks administration. Due to the different regimens applied in treatment cycles, Cmin of elotuzumab in combination with lenalidomide/dexamethasone increased in the initial 8 weeks (i.e. first 2 cycles, once weekly dose), and then decreased (Week 8 to Week 12) and reached steady state from Week 12 because elotuzumab is administered once for every two weeks after the first 2 cycles. Over the study periods, no notable increase in Cmin was observed.

The effect of disease status on pharmacokinetics of elotuzumab has been investigated in PPK analysis. PK of elotuzumab was not influenced by ECOG score, LDH or albumin. The PPK analysis showed that for patients in the highest quartile of baseline serum M-protein concentrations (3.2-7.7 g/dL), CavgSS, CmaxSS, and CminSS were > 30% lower (CminSS = 46% decrease) than the corresponding exposure values for patients in the lowest quartile of serum M-protein.

Special populations

Based on a population PK analysis using data from 375 patients, the clearance of elotuzumab increased with increasing body weight supporting a weight-based dose. The population PK analysis suggested that the following factors had no clinically important effect on the clearance of elotuzumab: age (37 to 88 years), gender, race, baseline LDH, albumin, renal impairment, and mild hepatic impairment (SmPC section 5.2).). No study in children has been conducted, as multiple myeloma is not expected to occur in children.

An open-label study (Study CA204007) evaluated the pharmacokinetics of elotuzumab in combination with lenalidomide and dexamethasone in patients with multiple myeloma with varying degrees of renal impairment (classified using the CrCL values). The effect of renal impairment on the pharmacokinetics of elotuzumab was evaluated in patients with normal renal function (CrCl > 90 mL/min; n = 8), severe renal impairment not requiring dialysis (CrCl <30 mL/min; n = 9), or end-stage renal disease requiring dialysis (CrCl < 30 mL/min; n = 9). No clinically important differences in the pharmacokinetics of elotuzumab were found between patients with severe renal impairment (with and without dialysis) and patients with normal renal function (SmPC sections 4.2, 5.2).

Empliciti is an IgG1 monoclonal antibody, which is principally cleared by catabolism. Thus, hepatic functional impairment is not likely to alter its clearance. The effect of hepatic impairment on the clearance of Empliciti was evaluated by population PK analyses in patients with mild hepatic impairment (total bilirubin [TB] $\leqslant$ the upper limit of normal [ULN] and AST > ULN or TB < 1 to 1.5 times ULN and any AST; n = 33). No clinically important differences in the clearance of Empliciti were found between patients with mild hepatic impairment and patients with normal hepatic function. Elotuzumab has not been studied in patients with moderate (TB > 1.5 to 3 times ULN and any AST) or severe hepatic impairment (TB > 3 times ULN and any AST) (SmPC sections 4.2, 5.2).

Table 4. Special Age Populations Treated with Elotuzumab in Pharmacokinetic Studies* (Pooled total number: 207/375)

PK Trials	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
CA204004 Phase 3, Randomized, Controlled, Multi-Center, Open Label Trial of Lenalidomide/Dexamethasone with or without Elotuzumab in Relapsed or Refractory Multiple Myeloma	117/313	64/313	1/313
CA204005 Phase 1, Open Label, Dose Escalation Study of Elotuzumab in Combination with Lenalidomide/Low-dose Dexamethasone in Patients with Relapsed or Refractory Multiple Myeloma in Japan	2/6	1/6	0/6
CA204007 Phase 1b, Multi-Center, Open-Label 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	4/25	4/25	1/25
CA204011 Phase 2 Biomarker Study of Elotuzumab (Humanized anti-CS1 Monoclonal IgG1 Antibody) Monotherapy to Assess the Association Between NK Cell Status and Efficacy in High Risk Smoldering Myeloma	7/31	1/31	0/31

*Includes subjects with evaluable PK in the population PK dataset

E-Ld: Elotuzumab combined with lenalidomide and dexamethasone
Ld: lenalidomide and dexamethasone

Pharmacokinetic interaction studies

No *in vitro* or *in vivo* studies on pharmacokinetic drug interactions have been submitted.

Pharmacokinetics using human biomaterials

Regarding immunogenicity, elotuzumab exposure in ADA positive patients was lower and is likely confounded by baseline M-protein levels. Development of antibodies started early in elotuzumab treatment was transient and resolved by 2 to 4 months. Clearance appeared to return to baseline at later time points when ADAs were no longer detected. The causal relationship between higher M-protein level and it's impact on efficacy and safety of elotuzumab could not be fully established. Further data regarding immunogenicity is in the Pharmacodynamics section.

2.4.3. Pharmacodynamics

Mechanism of action

The mechanism of action of elotuzumab shows that NK cell-mediated ADCC (antibody dependent cellular cytotoxicity) is a major component to the activity observed in vitro.

Elotuzumab directly activates natural killer cells through both the SLAMF7 pathway and Fc receptors enhancing anti-myeloma activity in vitro. Elotuzumab also targets SLAMF7 on myeloma cells and facilitates the interaction with natural killer cells to mediate the killing of myeloma cells through antibody-dependent cellular cytotoxicity (ADCC).

Primary and Secondary pharmacology

No clinical pharmacodynamic studies were submitted and clinical PD data were obtained from clinical efficacy and safety studies performed in patients with multiple myeloma (studies HuLuc63-1701; HuLuc63-1702; HuLuc63-1703; CA204004; CA204004; CA204011).

Pharmacodynamic assessments included percent saturation (receptor occupancy, RO) of SLAMF7, temporal changes in SLAMF7 expression in peripheral blood and bone marrow, temporal changes in T, B, and NK cells during the first course of treatment, temporal changes in cytokines/chemokines/ growth factors, baseline soluble SLAMF7 (sSLAMF7), and association of cell counts for major immune subsets and SLAMF7 expression in relation to clinical response as defined by EBMT criteria.

SLAMF7 receptor occupancy

The relationships between serum concentrations of elotuzumab and SLAMF7 RO on peripheral blood NK cells and bone marrow NK cells, as well as antigen rich CD45dim CD38+ and CD45dim CD138+ plasma cells was analysed in phase 1 elotuzumab monotherapy study HuLuc63-1701. In addition, the percentage RO of SLAMF7 by elotuzumab on CD38+ plasma cells versus elotuzumab serum concentrations is analysed in phase 1 study HuLuc63-1702 (elotuzumab + bortezomib) and phase 2 study HuLuc63-1703 (elotuzumab + lenalidomide/dexamethasone). All three clinical studies showed that more than 80% of SLAMF7 receptors were occupied when serum concentrations of elotuzumab reached between 10 to 100 µg/mL. In Study HuLuc63-1701, it was shown that at day 56 after a dose of 10.0 mg/kg, 100% occupation of SLAMF7 binding sites on peripheral blood NK cells and bone marrow NK cells, as well as on antigen rich CD45dimCD38+ and CD45dimCD138+ plasma cells was reached in all except one measurement in one individual.

Temporal changes in NK, T, B and SLAMF7+ NK Cells and Total Lymphocytes

In Study HuLuc63-1701 a transient decrease in natural killer (NK) cells, CD4+ cells, CD8+ cells, B cells, total lymphocytes, and SLAMF7+ NK cells was observed following the first dose of elotuzumab; whereas changes post fourth dose on Day 42 by comparison were modest. Results in studies HuLuc63-1702 and HuLuc63-1703 were similar to Study HuLuc63-1701. Changes in NK cell subsets were also observed on Day 22 (C2D1) and Day 29 (C2D1) in Study CA204011; however, no further assessment was conducted beyond Day 29. In study CA204009 (E-Bd), there was a general decline in total NK cells after initial doses of therapy observed at C2D1 for both groups. NK cells recovered to near baseline levels by the end of therapy in Study CA204009. The transient reduction in cell counts after the initial dose was associated with a transient increase in IP-10, a chemokine that stimulates migration of activated T cells and NK cells. There was no evidence of lymphocyte decreases associated with repeated dosing of elotuzumab *in vivo*.

Temporal changes in cytokines, chemokines and growth factors

In vitro: of the 22 cytokines, chemokines, and growth factors evaluated, only two, monocyte chemotactic protein 1 (MCP-1) and interferon gamma-induced protein 10 (IP-10), were significantly elevated by elotuzumab treatment in the majority of the donor samples. Eight additional cytokines, IL-2, IL-6, IL-8, IL-12(p40), IFNγ, MIP-1α, RANTES, and tumor necrosis factor-alpha (TNF-α), were statistically increased by elotuzumab treatment; however these elevations were observed in a minority of donors tested and/or the concentration increases were relatively low (less than 100 pg/mL) in the elotuzumab-treated samples. Nine cytokines, IL-1α, IL-1β, IL-3, IL-4, IL-12(p70), IL-13, IL-15, eotaxin, and GM-CSF, were not impacted by elotuzumab in the whole blood assay, and three cytokines, IL-5, IL-7, and IL-10, were not detected in any sample.

Since elotuzumab has the propensity to cause the release of cytokines in whole blood cultures *in vitro*, temporal changes in cytokines, chemokines, and growth factors were investigated in 3 phase 1 studies *in vivo* (HuLuc63-1701, HuLuc63-1702 and HuLuc63-1703). Most individuals showed an increase in three analytes: TNF-α, IP-10, and MCP-1 after initial elotuzumab administration and there was a trend for levels to return to baseline by Day 7. After subsequent elotuzumab doses, only some individuals showed an increase in the level of these cytokines, with the magnitude of response generally lower than that observed after the first dose.

Other analytes, interleukin 1α (IL-1α), IL-1Ra, IL-6, IL-8, IL-10, Fractalkine, granulocyte/macrophage colony-stimulating factor (GM-CSF), macrophage inflammatory protein 1α (MIP- 1α), and MIP-1ß, showed a similar pattern to what was observed for TNF-α, IP-10, and MCP-1. Results in studies HuLuc63-17024 and HuLuc63-17033 were similar to Study HuLuc63-170184.

Soluble serum protein assessments

Phase 1 studies HuLuc63-1701 and HuLuc63-1702 showed that a majority of patients (>67%) had measurable sSLAMF7 in serum at baseline. In Phase 2 study HuLuc63-1703 no relationship was observed between sSLAMF7 levels in serum at baseline and a patient's best overall response/PFS/tumor stage/ MM risk assessment as determined by individual cytogenetic analysis/ or serum M-protein levels at study entry. In Phase 2 study CA204011 both cohorts (10 and 20 mg/kg) showed similar and significant relative increase in total sSLAMF7 at C2D1, with Cohort 2 (10 mg/kg) showing a greater absolute increase in absolute sSLAMF7.

Association of cell count/ cell function and clinical response

In Phase 1 study HuLuc63-1701, no association was observed between baseline lymphocyte cell counts and subsequent diagnosis of "Stable Disease" at any visit up to nominal Day 56 of the first treatment cycle. Likewise, a relationship between Stable Disease and elotuzumab monotherapy treatment was not observed for NK, CD4+ T, B, monocytes, and CD8+ T cell counts, although this phase 1 dose escalation study was not powered to determine efficacy.

In study HuLuc63-1702, there was no meaningful correlation between cytotoxicity of the PBMC samples and clinical response.

In Phase 2 study CA204011, there was no meaningful association between the percentage of baseline CD56dim cells in bone marrow and objective response (minor [minimal] response or better) based on an analysis on all treated subjects. The results were not consistent, when examining the association between objective response and CD56dim cells in bone marrow for Cohort 1 (20 mg/kg; parameter estimate of 0.166) or Cohort 2 (10 mg/kg; parameter estimate of - 0.109) thereby making interpretation inconclusive.

Association of SLAMF7 expression and clinical response

In study HuLuc63-1701 individual patients were ranked according to the percentage of plasma cells that stained positive for SLAMF7 expression in bone marrow at baseline and subsequent best clinical response in the first treatment cycle (between Days 0 and 56). The median percentage SLAMF7 expression was 81% (n=17) in patients with stable disease, and 80% (n=15) with progressive disease, although ranges were very wide in both groups.

In study HuLuc63-1703 no relationship between SLAMF7 expression on plasma cells present in bone marrow aspirates at baseline and clinical response as defined by IMWG criteria or PFS was observed.

In vitro ADCC and Lymphocyte Subsets Depletion Studies

In order to confirm that elotuzumab would show anti-tumor activity at the concentrations identified in *in vitro* SLAMF7 receptor occupancy studies, ADCC of elotuzumab was investigated in several studies. In one study, the results showed that elotuzumab (10 µg/mL) induced specific myeloma-cell lysis in multiple assays using purified NK cells from healthy allogeneic donors or autologous NK cells from multiple myeloma donors as effectors. Similar results were obtained in another study using peripheral blood mononuclear cells (PBMC) as effectors. In this study, maximum lysis of tumor cells was observed at 0.1 µg /mL. However, some patient MM cells required elotuzumab concentrations as high as 100 µg /mL to inhibit proliferation and survival in the presence of BMSCs.

Depletion studies were carried out using whole blood samples from healthy donors. Samples were tested for depletion of T, NK, B, and memory B cells at elotuzumab concentration of 100 or 200 µg /mL. The results indicated no apparent effect of elotuzumab on total lymphocytes, T-, and B-cell counts and a modest effect on NK cells (20% decrease).

On in vitro challenge with elotuzumab in whole blood cultures from healthy donors, the increase in some cytokines may be lower or absent compared to that seen in the blood of subjects who have received elotuzumab.

Integrated analyses of the elotuzumab assessments for immunogenicity were performed for studies CA204004, CA204005, CA204007, and CA204009. Out of 390 elotuzumab-treated subjects across these studies, 9 subjects (2.3%) were ADA-positive at baseline, 72 subjects (18.5%) were ADA-positive on-study, and 318 subjects (81.5%) were ADA-negative. Of the 72 ADA-positive subjects, 2 subjects developed persistent ADA response (both were also neutralizing). NAbs were only characterized in Study CA204004 and it was found that 19 of 299 subjects in CA204004 trial had NAbs. Neutralizing antibodies for majority of the 19 subjects in study CA204004 developed during their 1st ADA assessment post elotuzumab administration, and were resolved by the 2nd ADA assessment. Also, only 3 of these 19 subjects were NAb-positive at more than 1 visit beyond their 2nd ADA assessment visit. Progression for most of these subjects occurred much later relative to the detection of ADA or NAbs.

In study CA204004, infusion reactions or hypersensitivity reactions following elotuzumab treatment were assessed. One-hundred and sixteen (116) subjects, when treated with E-Ld, with baseline and at least one post-baseline ADA assessment, experienced hypersensitivity or infusion reactions and 21 (18.1%) and 95 (81.9%) of these subjects were ADA-positive and ADA-negative, respectively. Of these 116 subjects with infusion or hypersensitivity reactions, 10 were NAb-positive subjects. In comparison, 88 subjects in the control arm experienced hypersensitivity. None of the subjects in the control arm had infusion reactions. ADAs in these subjects, and in general for IgGs don't occur until Day 21-28 after the administration of first dose of IgG, therefore a clear temporal or causal relationship to occurrence of ADAs and IRs cannot be established based on this limited data.

No clear association can be established between presence of ADA and loss of efficacy. The ORR in NAb-positive subjects was 78.9% (15 out of 19 subjects) compared to the overall ORR for the study, 78.5% (252 out of 321 subjects). In addition, the effect of immunogenicity on PFS was tested by adding categorical covariate ADA (equal to 1 for subjects with at least one positive ADA observation including baseline and equal to 0 otherwise) to the final E-R PFS model. Immunogenicity was found to not be statistically significant on the risk for disease progression.

In CA204009, of the 77 randomized subjects, 72 elotuzumab-treated subjects had evaluable ADA data at baseline and post baseline. Two subjects (2.8%) were ADA-positive at baseline, 20 subjects (27.8%) were ADA-positive on-study, and 52 subjects (72.2%) were ADA negative. Of the 20 ADA-positive subjects, 0 subjects developed persistent ADA.

In study CA204011 elotuzumab monotherapy, 29 subjects had evaluable data but samples were not assayed for NAb. In the 20 mg/kg cohort, 7 of 14 subjects had positive immunogenicity samples of which 2 were ADA persistent. In the 10 mg/kg cohort, 5 out of 15 subjects had on study positive immunogenicity samples and 1 of the 5 had ADA persistent response. The safety profiles of the 3 persistent positive subjects were not clinically different than those seen in ADA negative subjects. There were no acute infusion reactions, hypersensitivity events, new or additional AEs observed in these 3 subjects. Some of the subjects with an ADA-positive response had lower measured elotuzumab Cmin concentrations on days with ADA positive response. The ADA titers decreased and cleared in all but 4 subjects. There were no safety concerns among subjects with positive immunogenicity responses.

Overview of Effect of Elotuzumab on ECG Parameters

The effects of elotuzumab treatment on the ECG parameters, as well as AEs potentially related to ECG intervals, was assessed in elotuzumab-treated subjects from Phase 2 Study CA204011, which was a monotherapy study, and Phase 3 Study CA204004, which was in combination with lenalidomide/dexamethasone, who consented to participate in the ECG sub-study.
Results of the ECG analysis indicate that elotuzumab, at both dose levels of 10 and 20 mg/kg, does not have a clinically meaningful effect on ECG intervals, including QTc interval.

Study CA204011 (elotuzumab monotherapy)

QTcF interval
In study CA204011, no subject had a QTcF interval >480 msec or a ΔQTcF >60 msec across both dose levels. Few subjects had QTcF intervals or ΔQTcF intervals that exceeded the pre-specified ranges (QTcF > 450 msec; ΔQTcF > 30 msec) considered borderline or prolonged. Five subjects (2 in Cohort 1 [20 mg/kg] and 3 in Cohort 2 [10 mg/kg]) had a QTcF between > 450 to ≤ 480 msec. Three subjects in Cohort 2 had a ΔQTcF between > 30 to ≤ 60 msec.

PR interval: Four subjects in Cohort 1 (20 mg/kg) had values between > 200 to ≤ 220 msec and 3 subjects (2 subjects in Cohort 1 and 1 subject in Cohort 2 [10 mg/kg]), had a PR interval >220 msec.
PR interval change from baseline ≥ 25% was seen in 1 subject in Cohort 1.

QRS interval: Six subjects (2 subjects in Cohort 1 [20 mg/kg] and 4 subjects in Cohort 2 [10 mg/kg]) had QRS values >110 msec. One subject in Cohort 2 had a QRS interval change from baseline ≥ 25%.

Heart rate: 14 subjects (6 in Cohort 1, 8 in Cohort 2) had values ≥ 90 bpm and none had a HR ≤ 50 bpm.
Concentration - Response Relationship
There was no significant relationship between QTcF change from baseline and elotuzumab concentration. Moreover, the upper limit of the 90% CI for mean change in QTcF was less than 10 msec over the range of observed elotuzumab concentrations.

Three subjects had AEs that could potentially be related to ECG findings. One subject each had an AE of palpitation, tachycardia or syncope after treatment with 20 mg/kg elotuzumab.

Study CA204004

The effects of elotuzumab on ECG parameters, including QTc intervals were evaluated in elotuzumab-treated subjects who consented to participate in the ECG sub-study in Study CA204004.

The change in QTcF and ΔQTcF intervals post-infusion on Day 1 of Cycle 1 and Day 22 of Cycle 2 was < 10 msec compared to pre-dose values. On these Days, ΔQTcF intervals were associated with a large degree of variability (range -22.3 to 56.0 msec). Both QTcF and ΔQTcF values at predose (prior to elotuzumab infusion) on Days 1 and 8 of Cycle 1, Day 22 of Cycle 2, and Day 1 of Cycle 3 were somewhat prolonged compared to the -1.0 Hour (prior to pre-medication) or baseline value. However, elotuzumab infusion on Day 1 of Cycle 1 and Day 22 of Cycle 2 did not appreciably prolong the QTc interval further. The PR and QRS intervals were largely unchanged during the study, as was HR.

A formal categorical analysis was not done for this ECG sub-study due to the small number of participating subjects. Overall, no subject had a QTcF interval > 480 msec and no subject had a ΔQTcF > 60 msec during the study. Five subjects had ΔQTcF values ≥30 msec. Few subjects had a PR interval > 200 msec or a QRS interval > 110 msec during the study. No subject had a ΔPR or ΔQRS > 25% compared to baseline.

No subject that participated in the ECG sub-study had an AE that was thought to be potentially related to an abnormal ECG finding.

2.4.4. Discussion on clinical pharmacology

Overall, pharmacokinetics of elotuzumab is quite comparable with other monoclonal antibodies. The volume of distribution of elotuzumab approximately equals vascular space (3-6 L for a typical patient), consistent with the expected low distribution of mAbs. Also the observed clearance (13.2 mL/day/kg) and long elimination half-life (6-8 days) of elotuzumab were comparable with other chimeric IgG antibodies. The pharmacokinetics of elotuzumab is nonlinear due to binding of elotuzumab to the target. Due to depletion of the target upon treatment, steady-state clearance was driven by elimination of elotuzumab only from the central compartment. Only dose regimen of 10 mg/kg is proposed for the treatment of elotuzumab, thus dose proportionality is not relevant for efficacy and safety.

A reduction of 10% (from 100% to 90%) of patients reaching the target level after 8 weeks of treatment of elotuzumab in combination with lenalidomide/dexamethasone was due to the switching of dosing regimen from elotuzumab 10 mg/kg every week (QW) in Cycles 1 and 2 to every 2 weeks (Q2W) after Cycle 2. The 70 µg/ml target concentration was based on preclinical xenograft multiple myeloma mouse model, and it is more appropriate to discuss the clinical consequence of the 10% based on the exposure-response analysis for PFS. The justification for the absence of a causal relationship between elotuzumab exposure and efficacy (i.e. the risk of disease progression is confounded by baseline serum M-protein levels) by the applicant is acceptable.

For patients in the highest quartile of baseline serum M-protein concentrations (3.2-7.7 g/dL), CavgSS, CmaxSS, and CminSS were > 30% lower (CminSS = 46% decrease) than the corresponding exposure values for patients in the lowest quartile of serum M-protein. As PFS decreased along with the increase of M protein level and similar decrease of PFS was also observed in control group (without Empliciti), it is agreed that the clinical outcome (e.g. PFS) of the treatment of elotuzumab in combination with lenalidomide is largely dependent on the disease status (e.g. baseline M-protein). Therefore, an impact of a decrease in CminSS on efficacy cannot be concluded. In addition, increasing dose of elotuzumab (from

10 mg/kg to 20 mg/kg) did not improve the PFS in Study HuLuc63-1703. Drug exposure level in patients with the body weight > 99.8 kg did not differ from patients with lower body weight. Further, the safety profile (Study HuLuc63-1703) in patients treated with elotuzumab 20 mg/kg was similar with the patient with elotuzumab dose of 10 mg/kg, indicating that elotuzumab appears tolerable at doubled exposures. Therefore, risk of overexposure in obese patients was not anticipated.

Empliciti may be detected in the serum protein electrophoresis (SPEP) and serum immunofixation assays of myeloma patients and could interfere with correct assessment of the response classification. The presence of elotuzumab in patient's serum may cause a small peak in the early gamma region on SPEP that is IgGκ on serum immunofixation. This interference can impact the determination of complete response and possibly relapse from complete response in patients with IgG kappa myeloma protein. In case of detection of additional peaks on serum immunofixation, the possibility of a biclonal gammopathy should be excluded. (SmPC section 4.5).

As with all therapeutic proteins, there is a potential for immunogenicity to Empliciti. Of 390 patients across four clinical studies who were treated with Empliciti and evaluable for the presence of anti-product antibodies, 72 patients (18.5%) tested positive for treatment-emergent anti product antibodies by an electrochemiluminescent (ECL) assay. Neutralizing antibodies were detected in 19 of 299 patients in study CA204004. In the majority of patients, immunogenicity occurred early in treatment and was transient resolving by 2 to 4 months. There was no clear causal evidence of altered pharmacokinetic, efficacy, or toxicity profiles with anti-product antibody development based on the population pharmacokinetic and exposure-response analyses (SmPC section 4.8).

There was no elotuzumab dose or concentration-related effects on ECG intervals, including QTc interval, over the concentrations resulting from the investigated elotuzumab doses. In Study CA204011 (elotuzumab monotherapy) one subject each had an AE of palpitation, tachycardia or syncope after treatment with 20 mg/kg elotuzumab. Of the AEs in three subjects that might potentially be related to ECG findings, a causal relationship seems unlikely as a temporal relationship between the AE and ECG changes was not apparent. No subjects that participated in the Study CA204004 ECG sub-study had an AE that was thought to be potentially related to an abnormal ECG finding.

No effect of elotuzumab in combination with Ld or as a single agent was seen on QTc prolongation or AEs potentially related to ECG intervals. No data is available on changes of QTc interval or changes in ECGs for patients treated with E-Bd.

Conclusions on clinical pharmacology

In conclusion, pharmacokinetics and pharmacodynamics of elotuzumab has been investigated to a reasonable extent.

2.5. Clinical efficacy

2.5.1. Dose response studies

Dose finding

Clinical dose finding was performed in study HuLuc63-1703 for the combination E-Ld and in study HuLuc63-1702 for the combination E-Bd. The proposed dose of 10mg/kg as intravenous infusion until disease progression or unacceptable toxicity is based on these two studies.

Study HuLuc63-1703: Elotuzumab + Ld

Study HuLuc63-1703 was a phase 1b/2, multicenter, open-label, dose-escalation study. Objectives of this study were to identify the MTD of elotuzumab (phase 1 part) and to investigate its safety and efficacy when combined with lenalidomide and dexamethasone in patients with relapsed MM (phase 2 part).

In study HuLuc63 1703 (phase 1 part) elotuzumab was administered IV using escalating dose of 5, 10, or 20 mg/kg in combination with Ld. Elotuzumab schedule was modified from Q2W, as used in the previous monotherapy study, to a more intensive weekly administration for the first two 28-day cycles, in order to rapidly reach SLAMF7 saturation and targeted minimum elotuzumab concentration. The E-Ld combination was generally well tolerated and showed durable response rates. No MTD was observed up to the maximum dose of 20 mg/kg and the objective response rate (ORR) was 82%.

In the Phase 2 part of study HuLuc63-1703, subjects were randomized to receive elotuzumab 10 mg/kg or 20 mg/kg in combination with lenalidomide/dexamethasone. The E-Ld administration schedule was similar to the Phase 1 part of the study. E-Ld confirmed to be generally well tolerated and no apparent differences in the safety profile were observed between the 2 dose groups. A retrospective statistical analysis indicated no statistical evidence of treatment differences between the 10 mg/kg vs 20 mg/kg regimen in terms of ORR and progression-free survival (PFS). Furthermore, based on exposure-response (E-R) analyses, no definite conclusion could be 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. Since both efficacy and safety were generally comparable be-tween the 2 doses, the 10 mg/kg dose was carried forward to the phase 3 study and proposed for the E-Ld combination.

Table 5. Efficacy Parameters in Phase 2 Study HuLuc63-1703 (Phase 2 part)

Efficacy Parameter	10 mg/kg (N = 36)	20 mg/kg (N = 37)	Total (N = 73)
ORR, N (%)	33 (92)	28 (76)	61 (84)
Median TTR (months)	1.0	1.7	1.0
Median DOR (months)	34.8	29.0	29.2
Median PFS (months)	32.5	25.0	28.6

Abbreviations: ORR = objective response rate; TTR = time to response; DOR = duration of response; PFS = progression free survival.

Study HuLuc63-1702: Elotuzumab + Bd

Study HuLuc63-1702 was a phase 1/2, multicenter, open-label, dose-escalation study investigating the MTD of elotuzumab and its safety and efficacy when combined with bortezomib.

Phase 1 study HuLuc63-1702 tested IV elotuzumab in combination with bortezomib. Subjects with relapsed/refractory MM were treated with escalating dose of 2.5, 5, 10, or 20 mg/kg of elotuzumab on Days 1 and 11 in 21-day. The combination of elotuzumab and bortezomib was generally well tolerated: MTD was not reached up to the maximum planned dose of 20 mg/kg and the safety profile did not appear to be dose dependent. While data were limited, subjects dosed with 10 or 20 mg/kg showed ≥ 80% saturation of SLAMF7 receptors when corresponding target drug levels were ≥ 100 µg/mL. From the efficacy point of view, all efficacy parameters were numerically higher for the 10 mg/kg dose compared to the other doses. The 10 mg/Kg dose was therefore chosen for the phase II study CA204009 which investigated the combination of elotuzumab with the standard of care regimen of bortezomib/dexamethasone (E-Bd) in subjects with relapsed MM. The selected elotuzumab administration schedule was based on the schedule previously used in the phase 1 Study HuLuc63-1702, modified in order to more closely match the schedule employed with E-Ld in phase 3 Study CA204004

(i.e. elotuzumab weekly administration in cycles 1 and 2). The combination E-Bd was overall well tolerated and no meaningful increase in AEs was observed. Therefore, the 10mg/kg dose and the administration schedule used in study CA204009 was proposed for the E-Bd combination.

Table 6Efficacy Parameters in Study HuLuc63-1702

Efficacy Parameter	2.5 mg/kg (N = 3)	5 mg/kg (N = 3)	10 mg/kg (N = 3)	20 mg/kg (N = 18)	Total (N = 27)
ORR, N (%)	2 (66.7)	0	3 (100.0)	8 (44.4)	13 (48.1)
Median TTR (months)	1.1	NA	3.0	1.9	2.1
Median DOR (months)	5.9	NA	9.1	4.2	6.6
Median PFS (months)	9.4	NA	24.5	7.8	9.4

Abbreviations: ORR = objective response rate; TTR = time to response; DOR = duration of response; PFS = progression free survival (also known as TTP); NA = not applicable.

Source: Refer to Table 3.4.2.3-1 of Module 2.7.2 Elotuzumab SCP[21]

Across the dose response studies, dose escalation up to 20 mg/kg (range: 2.5-20 mg/kg) was achieved without reaching a maximum tolerated dose. Efficacy at an elotuzumab dose of 20 mg/kg appears to be less than with 10 mg/kg. Based on saturation of SLAMF7, PK of elotuzumab, the safety/efficacy profile, and FDA feedback, the 10 mg/kg elotuzumab dose was selected for further clinical development. Saturation of elotuzumab binding may explain lack of increasing efficacy with increasing dose, but especially for the combination E-Bd this must be interpreted with caution as there were only 3 subjects in each of the other dose cohorts and 18 subjects in the 20 mg/kg cohort. Overall, these data do support not using an elotuzumab dose higher than 10 mg/kg.

2.5.2. Main studies

Study CA204004

This was a phase 3, randomized, open-label trial investigating the combination of elotuzumab with lenalidomide plus low-dose dexamethasone (E-Ld) versus lenalidomide plus low-dose dexamethasone alone (Ld) in subjects with previously treated relapsed or refractory MM.

Methods

Study Participants

Inclusion criteria

- ≥ 18 years of age
- Eastern Cooperative Oncology group (ECOG) performance status ≤2
- Documented evidence of MM and received 1 to 3 prior lines of therapy with documented progression by EBMT criteria after the most recent therapy; AND
- Measurable disease as defined by at least 1 of the following:
    - Serum IgG, IgA or IgM M-protein ≥0.5 g/dL or serum IgD M-protein ≥0.05 g/dL OR
    - Urine M-protein ≥ 200 mg excreted in a 24-hour collection sample
- Prior lenalidomide exposure was permitted only if they fulfilled all of the following:
    - Best response achieved was ≥ partial response (PR)
    - Were not refractory to prior lenalidomide therapy (defined as no progression while receiving lenalidomide or within 9 months of last dose of lenalidomide)
    - Subject did not discontinue lenalidomide due to a Grade ≥3 related adverse event (AE)
    - Subject did not receive more than 9 cycles of lenalidomide and had at least 9 months between the last dose of lenalidomide and progression

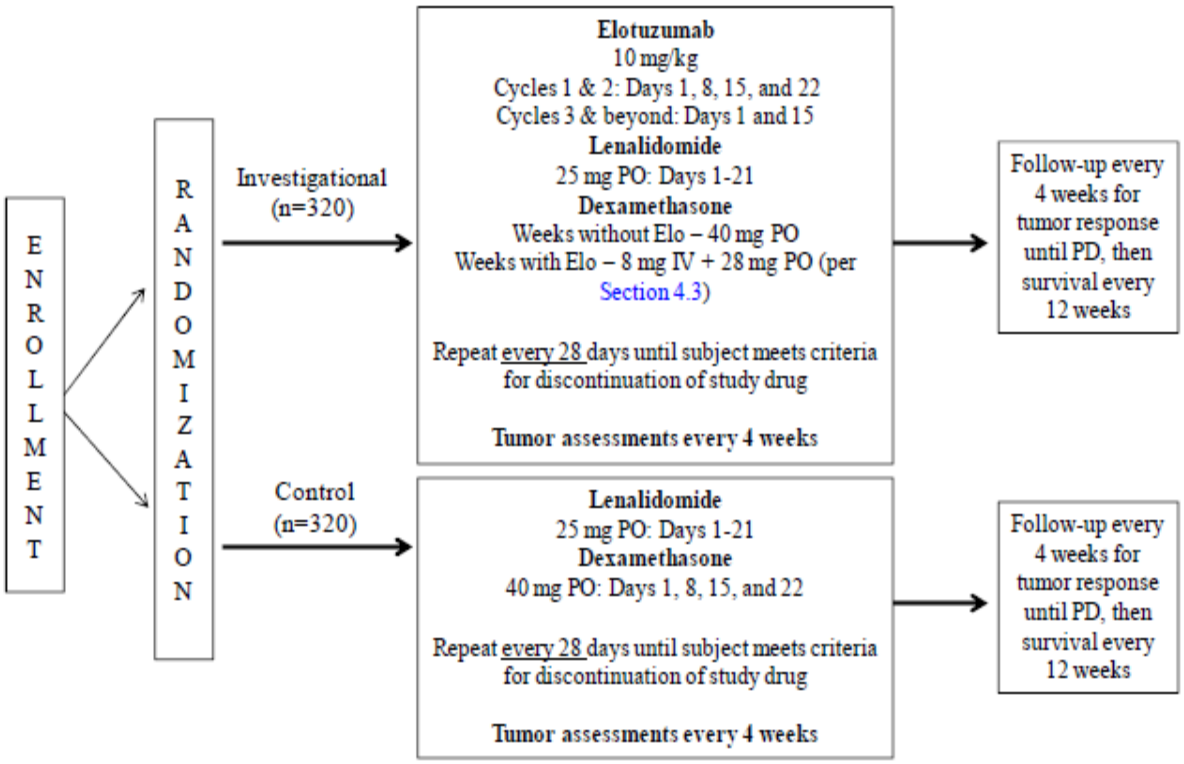
Exclusion criteria

- Non-secretory or oligo-secretory of serum free light-chain only myeloma
- Active plasma cell leukemia
- Prior therapy with elotuzumab or any IMiD (including pomalidomide), except for prior thalidomide or lenalidomide
- Refractory to prior lenalidomide
- Administration of chemotherapy, biological, immunotherapy, or investigational agent (therapeutic or diagnostic) within 3 weeks prior to randomization (14 days for non-myelosuppressive therapy). Subjects should be 6 weeks from last dose of nitrosourea, nitrogen mustards, melphalan or monoclonal antibody, 12 weeks from autologous stem cell transplant (SCT), and 16 weeks from allogeneic SCT.
- All AEs of any prior chemotherapy, surgery, or radiotherapy not resolved to Grade ≤2
- Significant cardiac disease
- Prior cerebrovascular event with persistent neurologic deficit
- Any medical conditions that, in the investigator's opinion, would impose excessive risk to the subject. Examples included: any uncontrolled disease, such as pulmonary disease, infection, seizure disorder; active infection that requires parenteral anti-infective treatment; any significant cardiac disease (including known or suspected cardiac amyloidosis); any altered mental status or and psychiatric condition that would interfere with the understanding of the informed consent
- Prior or concurrent malignancy, except any malignancy from which the subject the subject has been disease-free for > 5 years or adequately treated basal cell or squamous cell skin cancer
- Unable to tolerate thromboembolic prophylaxis
- Laboratory test findings:
    - Corrected serum calcium ≥ 11.5 mg/dL
    - Absolute neutrophil count < 1000 cells/mm3. No growth factors allowed within 1 week of enrolment
    - Platelets < 75,000 cell/mm3 (75 x 109/L)
    - Hemoglobin < 8 g/dL
    - Creatinine clearance < 30 mL/minute measured by 24-hour urine collection or estimated by the Cockcroft-Gault formula
    - Total bilirubin > 1.5 x upper limit of normal (ULN)
    - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥3 x ULN

Treatments

An overview of dose, regimen and follow up for each treatment group is shown in Figure 3.

Figure 1. Study Schema (Study CA204004)



Elotuzumab was administered intravenously (IV) at a dose of 10 mg/kg weekly (Days 1, 8, 15, and 22 of a 4-week cycle) of the first 2 cycles and every 2 weeks (Day 1 and Day 15) thereafter. No dose reduction was allowed for elotuzumab.

Lenalidomide was administered daily at a dose of 25 mg PO on Days 1-21 at least 2 hours after completion of elotuzumab. Lenalidomide dose adjustments were handled according to current medical practice.

Dexamethasone was administered weekly at a dose of 40 mg PO. During weeks of elotuzumab administration, dexamethasone was administered as a split dose of 28 mg PO + 8 mg IV 3 to 24 hours and at least 45 minutes, respectively, prior to elotuzumab infusion. IV dexamethasone was increased to 10 mg in case of previous grade 2 infusion reactions during the administration of elotuzumab, or 18 mg for subjects with grade 3 or recurrent grade 2 infusion reactions. To prevent imbalance in dexamethasone exposure between the two arms in the study, on the weeks that subjects received premedication with 18 mg IV dexamethasone, they only received a total of 16 mg oral dexamethasone.

In addition to IV dexamethasone, to prevent infusion reactions (IR) the following premedication regimen was administered 30 - 90 minutes prior to any elotuzumab dose:

- H1 blocker: diphenhydramine (25 - 50 mg PO or IV) or equivalent
- H2 blocker: ranitidine (50 mg IV) or equivalent
- acetaminophen (650 - 1000 mg PO).

If prior infusion reactions occurred, subjects received H1, H2 blockers and acetaminophen at maximum doses specified (i.e., 50 mg diphenhydramine, 50 mg ranitidine, and 1000 mg acetaminophen).

Subjects were also required to receive thromboembolic prophylaxis (e.g., aspirin, low molecular weight heparin, and vitamin K antagonists), per institutional guidelines.

Objectives

The primary objective of the study was to compare the progression free survival (PFS) and objective response rate (ORR) of E- Ld versus Ld alone.

Secondary objectives included the comparison of overall survival (OS) between the two treatment arms and the evaluation of the change from baseline of the mean score of pain severity and pain interference using the Brief Pain Inventory Short Form (BPI-SF) of E-Ld versus Ld.

Exploratory objectives included the assessment of safety in each arm; Time to tumour response (TTR) and duration of response (DOR); PFS rates at 1, 2 and 3 years; OS rates at 3, 4, 5 and 6 years; Health related quality of life (HrQoL) outcomes (EORTC QLQ-C30, EORTC QLQ-MY20 and BPI-SF, the measurement of serum concentrations of elotuzumab in the presence of lenalidomide and dexamethasone and the evaluation of the immunogenicity of elotuzumab.

Outcomes/endpoints

The primary efficacy endpoint was PFS defined as the time from randomization to the date of the first documented tumour progression or death due to any cause as determined by independent review committee (IRC) using EBMT criteria.

The co-primary endpoint was ORR defined as the proportion of randomized subjects who have either partial response or complete response as determined by IRC using the EBMT criteria.

Secondary efficacy endpoints

- Overall survival defined as the time from randomization to the date of death from any cause.

- Brief Pain Inventory Short Form, as a patient reported outcome assessed at screening, on day 1 of each cycle and at the end of treatment.

Exploratory efficacy endpoints

- Time to tumour response, defined as the time from randomization to the first objective documentation of PR or better.

- Duration of response, as measured from the time that the criteria for objective response are first met until the date of a progression event/death.

- Progression free survival rates at 1, 2 and 3 years.

- Overall survival rates at 3, 4, 5 and 6 years.

- European Organization for Research and Treatment of Cancer Quality of life Questionnaire (EORTC QLQ-C30), European Organization for Research and Treatment of Cancer Quality of life myeloma-specific module (EORTC-QLQ-MY20) and the Brief Pain Inventory- Short Form (BPI-SF).

Sample size

Approximately 640 patients were planned to be randomized. Overall alpha (0.05 two-sided) was split over the two primary endpoints as 0.005 for ORR and 0.045 for PFS.

With 640 subjects the test for the ORR would have 88.5% power at the 2-sided alpha level of 0.5% when the true odds ratio of the experimental to the control arm is 2 (i.e. when the response rate in the control arm is 60% and 75% in the experimental).

In total 466 PFS events were planned for the primary efficacy analysis of PFS to ensure that a 2-sided test procedure at significance level 0.045 within 1 interim analysis will have 88.7% power if the median PFS times in the control and experimental arms are 11.1 and 15 months, respectively, i.e., if the hazard ratio of the experimental arm to control arm is 0.74.

Randomisation

Subjects were randomized to either E-Ld or Ld alone in a 1:1 ratio using an interactive voice response system (IVRS). The randomization was stratified by the following factors: β2 microglobulin (< 3.5 versus ≥ 3.5 mg/L)**;** Number of prior lines of therapy (1 versus 2 or 3) and Prior IMiD (no vs prior thalidomide only vs other)

No more than 10% of subjects with prior lenalidomide therapy were allowed to be enrolled and this restriction was implemented using the IVRS.

Blinding (masking)

This was an open-label study.

Statistical methods

The ORR (per IRC) and PFS (per IRC) were selected as co-primary endpoints. If either of these two analyses achieved the level of significance (2-sided 0.5% for ORR or 2-sided 4.5% for PFS to preserve the overall type-I error for the study at the 5% level), the corresponding primary objective could be declared statistically significant.

No interim analysis of ORR was planned. A PFS interim analysis was planned when 70 % of the events would have been observed (i.e. 326 events of the planned 466 events) and after a minimum follow-up of 2 years from LPFV.

Crossover was not permitted at any time during the study. The number of events and power for PFS were calculated assuming an exponential distribution for each arm. The alpha level for PFS was adjusted for the planned interim analysis (IA) using Lan-DeMets α spending function with the O'Brien-Fleming type of boundary and is calculated based on the actual number of events observed at the time of analysis. If there were exactly 326 events, the DMC could recommend stopping the study for superior PFS if the two-sided p-value is ⩽ 0.0128. An observed hazard ratio of 0.7581 or less would result in a statistically significant difference at the IA. A hazard ratio of 0.7581 would translate to a 3.5 months improvement in median PFS (11.1 vs. 14.6 months). In case the study was stopped at the PFS IA because of superior PFS, randomized subjects would continue to be followed until the survival data were mature.

The nominal significance level for the final look, after 466 progression events, would be 0.0411. An observed hazard ratio of 0.8269 or less at the final analysis would result in a statistically significant difference and it would translate to a 2.3 months improvement in median PFS.

At database lock, 384 PFS events, corresponding to 82.4% of the 466 required events, were achieved, based on which the adjusted alpha level is 0.0239 (obtained using the Lan-DeMets α spending function with the O'Brien-Fleming type of boundary).

Primary analysis of PFS was per IRC based EBMT criteria with the following (censoring) scheme:

- Clinical deterioration is not considered progression.
- Subsequent systemic anti-myeloma therapy prior to documented progression is censored (at last tumor assessment before or on initiation of therapy

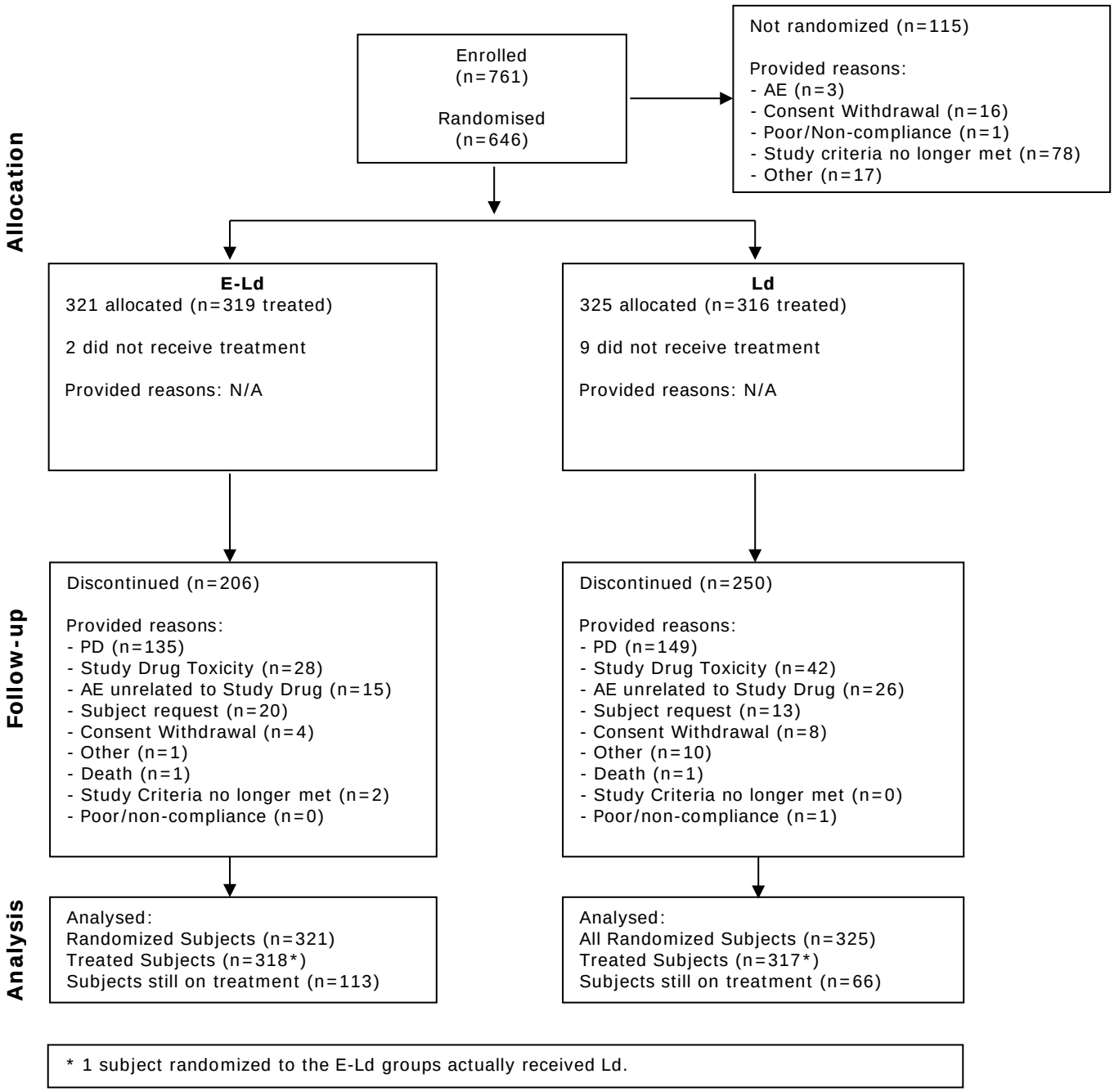
- Subjects with event (death or progression) > 10 weeks (2 missed visits) after previou adequate tumor assessment will be censored on that last adequate tumor assessment
- Subjects with no post-baseline tumor assessments and not die within 10 weeks after randomisation will be censored at date of randomisation

Supportive analyses for PFS included: ITT analysis per IRC of PFS; PFS per investigator using primary censoring scheme; PFS per investigator using ITT censoring scheme; A multivariate analysis (stratification factors and age, gender, ECOG, prior stem transplantation, high risk myeloma, time from diagnosis, creatine clearance, LDH; unstratified log rank test; and stratified analysis according to baseline CRF instead of IVRS.

Supportive and sensitivity analyses for ORR included: ORR by IRC using only data on randomized treatment (i.e., not counting best response during subsequent therapies); ORR using investigator assessment of best response; idem with not counting best response during subsequent therapies and ORR with 95%-CI using Clopper-Pearson methods

Results

Participant flow



* 1 subject randomized to the E-Ld groups actually received Ld.

Recruitment

The study was conducted in 230 sites in 21 countries. Patients were from Europe (60%), North America (21%), Japan (9%) and the rest of the world (10%, Australia, Israel).

The first patient first visit (FPFV) was on 14 June 2011, enrolment was completed on 20 November 2012 and the last patient last visit (LPLV) occurred on 1 September 2014.

Conduct of the study

The original study protocol was dated 14 October 2010 and was subsequently amended 12 times. The major changes were as follows:

Protocol amendment dated 27 January 2011

- Interim analysis comparison of PFS for early stopping for efficacy or futility at 50% of events removed
- Limited prior lines of therapy to 1 – 3 (original protocol allowed 1 – 4).
- Require at least 9 months between last dose of prior lenalidomide and disease progression (original protocol required at least 4 months).
- Limit prior exposure to lenalidomide to no more than 9 months (no prior limit in original protocol).
- Limit prior lenalidomide to no more than 10% of randomized subjects (no prior limit in original protocol).

Protocol amendment dated 15 March 2012

- Clarification of subject eligibility or study procedures
- Instructions for what should be done with missed doses of lenalidomide or dexamethasone.
- Revisions are made to exclusion criteria for clarity and consistency throughout the development program.

Administrative letter dated 23 May 2012

- Correction of oral dexamethasone dose adjustment for elotuzumab arm from 10 to 12 mg.

Protocol amendment dated 14 April 2014

- Addition of formal interim analysis, including required revisions to the power, endpoint definitions and efficacy analyses due to the addition of the interim analyses.
- A change in the hierarchy of the statistical analysis by including ORR as a co-primary endpoint with PFS
- The addition of a secondary objective comparing pain severity and interference using BPI-SF, and removal as exploratory objective.
- The addition of an exploratory objective to estimate the PFS rates at 1, 2, 3 years and the OS rates at 3, 4, 5 and 6 years.

Protocol amendment dated 7 May 2014

- Elotuzumab infusion rate escalation plan added to decrease the infusion of elotuzumab to approximately 1 hour

- Broadening of the medications that can be used for thromboprophylaxis.

Baseline data

Demographic, baseline disease characteristics and previous anti-cancer regimens are shown in Table 12, Table 13 and Table 14 respectively.

Table 7. Demographic Characteristics – All Randomized Patients (Study CA204004)

	E-Ld N = 321	Ld N = 325	Total N = 646
AGE (YEARS)			
N	321	325	646
MEAN	66.2	65.3	65.7
MEDIAN	67.0	66.0	66.0
MIN , MAX	37 , 88	38 , 91	37 , 91
Q1 , Q3	60.0 , 73.0	58.0 , 73.0	59.0 , 73.0
STANDARD DEVIATION	9.34	10.26	9.81
AGE CATEGORIZATION (%)			
< 65	134 (41.7)	142 (43.7)	276 (42.7)
>= 65 AND < 75	119 (37.1)	122 (37.5)	241 (37.3)
>= 75	68 (21.2)	61 (18.8)	129 (20.0)
GENDER (%)			
MALE	192 (59.8)	193 (59.4)	385 (59.6)
FEMALE	129 (40.2)	132 (40.6)	261 (40.4)
RACE (%)			
WHITE	264 (82.2)	280 (86.2)	544 (84.2)
BLACK OR AFRICAN AMERICAN	13 (4.0)	10 (3.1)	23 (3.6)
AMERICAN INDIAN OR ALASKA NATIVE	0	0	0
ASIAN	33 (10.3)	31 (9.5)	64 (9.9)
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	1 (0.3)	0	1 (0.2)
OTHER	9 (2.8)	4 (1.2)	13 (2.0)
NOT REPORTED	1 (0.3)	0	1 (0.2)
ETHNICITY (%)			
HISPANIC OR LATINO	5 (1.6)	1 (0.3)	6 (0.9)
NOT HISPANIC OR LATINO	28 (8.7)	33 (10.2)	61 (9.4)
NOT REPORTED	288 (89.7)	291 (89.5)	579 (89.6)

Table 8. Baseline Disease Characteristics (Study CA204004)

	E-Ld N = 321	Ld N = 325	Total N = 646
M-PROTEIN, SERUM (QUANTITATIVE SPE) (G/L)			
N	321	325	646
MEAN	23.9	25.1	24.5
MEDIAN	21.0	23.0	22.0
MIN , MAX	0 , 77	0 , 78	0 , 78
Q1 , Q3	12.0 , 35.0	14.0 , 35.0	13.0 , 35.0
STANDARD DEVIATION	16.21	15.41	15.81
M-PROTEIN, URINE (G/DAY)			
N	319	325	644
MEAN	0.401	0.414	0.408
MEDIAN	0.020	0.020	0.020
MIN , MAX	0.00 , 12.13	0.00 , 9.01	0.00 , 12.13
Q1 , Q3	0.000 , 0.230	0.000 , 0.360	0.000 , 0.280
STANDARD DEVIATION	1.0969	0.9253	1.0132
NUMBER OF LYTIC BONE LESIONS			
0	107 (33.3)	97 (29.8)	204 (31.6)
1 - 3	47 (14.6)	47 (14.5)	94 (14.6)
> 3	162 (50.5)	177 (54.5)	339 (52.5)
UNKNOWN	0	1 (0.3)	1 (0.2)
NOT REPORTED	5 (1.6)	3 (0.9)	8 (1.2)
PLASMACYTOMA			
YES	22 (6.9)	36 (11.1)	58 (9.0)
NO	241 (75.1)	226 (69.5)	467 (72.3)
UNKNOWN	0	2 (0.6)	2 (0.3)
NOT REPORTED	58 (18.1)	61 (18.8)	119 (18.4)
MIELOMA TYPE			
IGG	218 (67.9)	234 (72.0)	452 (70.0)
IGA	69 (21.5)	62 (19.1)	131 (20.3)
IGM	1 (0.3)	1 (0.3)	2 (0.3)
IGD	3 (0.9)	5 (1.5)	8 (1.2)
LIGHT CHAIN DISEASE	27 (8.4)	20 (6.2)	47 (7.3)
BICLONAL	2 (0.6)	3 (0.9)	5 (0.8)
NOT CLASSIFIED	1 (0.3)	0	1 (0.2)
ISS STAGE			
STAGE I	141 (43.9)	138 (42.5)	279 (43.2)
STAGE II	102 (31.8)	105 (32.3)	207 (32.0)
STAGE III	66 (20.6)	68 (20.9)	134 (20.7)
NOT REPORTED	12 (3.7)	14 (4.3)	26 (4.0)

Table 9. Previous Anti-Cancer Regimens

	E-Ld N = 321	Ld N = 325	Total N = 646
RESPONSE TO MOST RECENT LINE OF THERAPY			
REFRACTORY	113 (35.2)	114 (35.1)	227 (35.1)
RELAPSED	207 (64.5)	211 (64.9)	418 (64.7)
UNKNOWN	1 (0.3)	0	1 (0.2)
NUMBER OF SUBJECTS WITH AT LEAST ONE PRIOR SYSTEMIC THERAPY	321 (100.0)	325 (100.0)	646 (100.0)
NUMBER OF REGIMENS			
MEDIAN	2.0	2.0	2.0
MIN , MAX	1 , 4	1 , 4	1 , 4
NUMBER OF REGIMENS			
1	151 (47.0)	159 (48.9)	310 (48.0)
2	118 (36.8)	114 (35.1)	232 (35.9)
3	51 (15.9)	51 (15.7)	102 (15.8)
>3	1 (0.3)	1 (0.3)	2 (0.3)
PRIOR THERAPY			
STEM CELL TRANSPLANT	167 (52.0)	185 (56.9)	352 (54.5)
RADIOTHERAPY	90 (28.0)	61 (18.8)	151 (23.4)
SURGERY	36 (11.2)	35 (10.8)	71 (11.0)
REGIMEN			
BORTEZOMIB/DEXAMETHASONE	62 (19.3)	64 (19.7)	126 (19.5)
CYCLOPHOSPHAMIDE/DEXAMETHASONE/THALIDOMIDE	24 (7.5)	34 (10.5)	58 (9.0)
BORTEZOMIB/CYCLOPHOSPHAMIDE/DEXAMETHASONE	23 (7.2)	34 (10.5)	57 (8.8)
MELPHALAN/PREDNISONE/THALIDOMIDE	28 (8.7)	18 (5.5)	46 (7.1)
DEXAMETHASONE/THALIDOMIDE	13 (4.0)	24 (7.4)	37 (5.7)
DEXAMETHASONE/DOXORUBICIN/VINCRISTINE	19 (5.9)	15 (4.6)	34 (5.3)
OTHER	266 (82.9)	257 (79.1)	523 (81.0)
DRUGS			
ANTINEOPLASTIC & IMMUNOMODULATING AGENT	318 (99.1)	321 (98.8)	639 (98.9)
ANTINEOPLASTIC AGENTS	317 (98.8)	319 (98.2)	636 (98.5)
BORTEZOMIB	219 (68.2)	231 (71.1)	450 (69.7)
MELPHALAN	220 (68.5)	197 (60.6)	417 (64.6)
CYCLOPHOSPHAMIDE	154 (48.0)	163 (50.2)	317 (49.1)
DOXORUBICIN	102 (31.8)	95 (29.2)	197 (30.5)
VINCRISTINE	80 (24.9)	71 (21.8)	151 (23.4)
ETOPOSIDE	18 (5.6)	24 (7.4)	42 (6.5)
CISPLATIN	8 (2.5)	12 (3.7)	20 (3.1)
CARMUSTINE	9 (2.8)	9 (2.8)	18 (2.8)
DOXORUBICIN LIPOSOMAL	7 (2.2)	9 (2.8)	16 (2.5)
INVESTIGATIONAL ANTINEOPLASTIC	7 (2.2)	8 (2.5)	15 (2.3)
EPIRUBICIN	8 (2.5)	6 (1.8)	14 (2.2)
IDARUBICIN	7 (2.2)	5 (1.5)	12 (1.9)
IFOSFAMIDE	6 (1.9)	6 (1.8)	12 (1.9)
BENDAMUSTINE	3 (0.9)	5 (1.5)	8 (1.2)
CYTARABINE	4 (1.2)	3 (0.9)	7 (1.1)
CARFILZOMIB	2 (0.6)	1 (0.3)	3 (0.5)
RANIMUSTINE	3 (0.9)	0	3 (0.5)
ANTINEOPLASTIC	0	2 (0.6)	2 (0.3)
DAUNORUBICIN	1 (0.3)	1 (0.3)	2 (0.3)
FLUDARABINE	1 (0.3)	1 (0.3)	2 (0.3)
METHOTREXATE	1 (0.3)	1 (0.3)	2 (0.3)
ANTHRACYCLINE	1 (0.3)	0	1 (0.2)
ARAC/CISPLT/ETOP/METPRED	0	1 (0.3)	1 (0.2)
BUSULFAN	1 (0.3)	0	1 (0.2)
CARBOPLATIN	0	1 (0.3)	1 (0.2)
CYPHOS/DEXA/DOXRUB/VINCRI	1 (0.3)	0	1 (0.2)
PIRARUBICIN	0	1 (0.3)	1 (0.2)
VINORELBINE	0	1 (0.3)	1 (0.2)
VORINOSTAT	1 (0.3)	0	1 (0.2)
IMMUNOSUPPRESSIVE AGENT	16 (5.0)	21 (6.5)	37 (5.7)
LENALIDOMIDE	16 (5.0)	21 (6.5)	37 (5.7)
PSYCHOLEPTIC	153 (47.7)	157 (48.3)	310 (48.0)
THALIDOMIDE	153 (47.7)	157 (48.3)	310 (48.0)

Numbers analysed

The analysis populations of Study CA204004 are summarized in Table 15.

Table 10 Analyses populations (Study CA204004)

Datasets	E-Ld, N	Ld, N	Total
Enrolled: all subjects who signed the informed consent and who were entered in the IVRS	-	-	761
Randomized: all subjects randomized to any treatment group	321	325	646
Treated: all randomized subjects with at least one dose of study drug	318[a]	317[a]	635
ECG-evaluable: elotuzumab-treated subjects who consented to participate in the ECG substudy with a baseline ECG measurement and at least one on-study ECG measurement	10	-	10
PK-evaluable: all subjects with at least one dose of elotuzumab and at least one available serum elotuzumab concentration value	318	-	318

[a] As noted in Table 5-1.1, there was 1 subject randomized to E-Ld treatment but who received Ld treatment.
Abbreviations: IVRS, interactive voice response system; ECG, electrocardiogram; PK, pharmacokinetic, N, number of subjects

Outcomes and estimation

Co-Primary endpoint: PFS

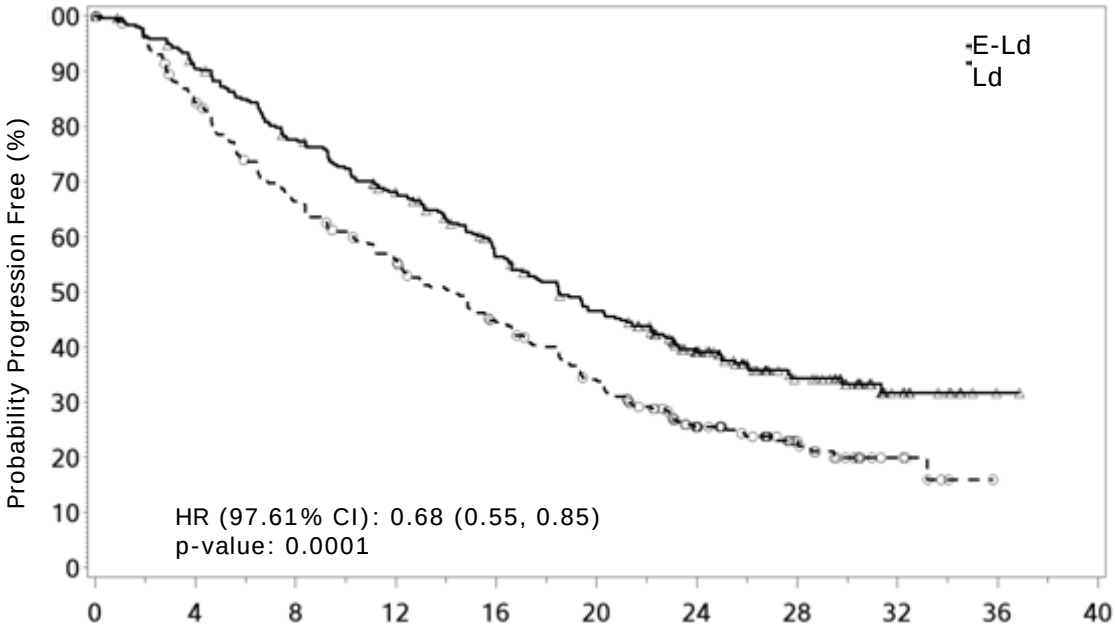
Results in terms of Progressive-Free Survival assessed by IRC and per Investigator are reported in Table 16 and in Figure 4.

Table 11. PFS Results per IRC and per Investigator by Primary and ITT Definitions (Study CA204004)

	PFS (Primary Definition)				**PFS (Intent-to-Treat Definition)**			
	IRC		**Investigator**		**IRC**		**Investigator**	
Parameter	**E-Ld**	**Ld**	**E-Ld**	**Ld**	**E-Ld**	**Ld**	**E-Ld**	**Ld**
Number of events (%)	179 (56)	205 (63)	167 (52)	201 (62)	192 (60)	231 (71)	181 (56)	226 (70)
Hazard ratio (95% CI)	0.70 (0.57-0.85)		0.65 (0.53-0.80)		0.68 (0.56-0.83)		0.64 (0.53-0.79)	
P-value	**0.0004**		**<0.0001**		**0.0001**		**<0.0001**	
1-year PFS (95% CI)	68% (63%, 73%)	57% (51%, 62%)	72% (66%, 77%)	61% (55%, 66%)	68% (63%, 73%)	56% (50%, 61%)	71% (65%, 75%)	59% (54%, 65%)
2-year PFS (95% CI)	41% (35%, 47%)	27% (22%, 33%)	47% (41%, 52%)	31% (25%, 36%)	39% (34%, 45%)	26% (21%, 31%)	45% (40%, 51%)	29% (24%, 34%)
3-year PFS (95% CI)	26% (20%, 31%)	18% (13%, 24%)	33% (27%, 38%)	21% (16%, 26%)	23% (18%, 28%)	15% (10%, 20%)	31% (26%, 36%)	18% (14%, 23%)
mPFS, months	19.4	14.9	22.7	16.7	18.5	14.3	21.4	16.5

Abbreviations: CI= confidence interval, IRC= International Review Committee, PFS= progression-free survival

Figure 2. Kaplan-Meier Plot of PFS- IRC - All Randomized Subjects (CA204004)



Progression Free Survival (Months)

Number of Subjects at Risk

E-Ld	321	282	240	206	164	133	87	43	12	1
Ld	325	262	204	168	130	97	53	24	7	

Subgroups: Key Efficacy Data by Lines of Therapy and Prior Therapy- CA204004

In order to have better understanding of which patients are most likely to benefit from treatment with the combination of elotuzumab with lenalidomide and dexamethasone, the absolute values of key parameters such as PFS, ORR, OS were provided for subgroups pre-defined according to the number of prior regimens and type of agents with which patients have previously been treated.

The numbers of patients per subgroup and the key parameters are shown in the tables below.

Table 12. Numbers of patients per subgroup of prior therapy in Study CA204004

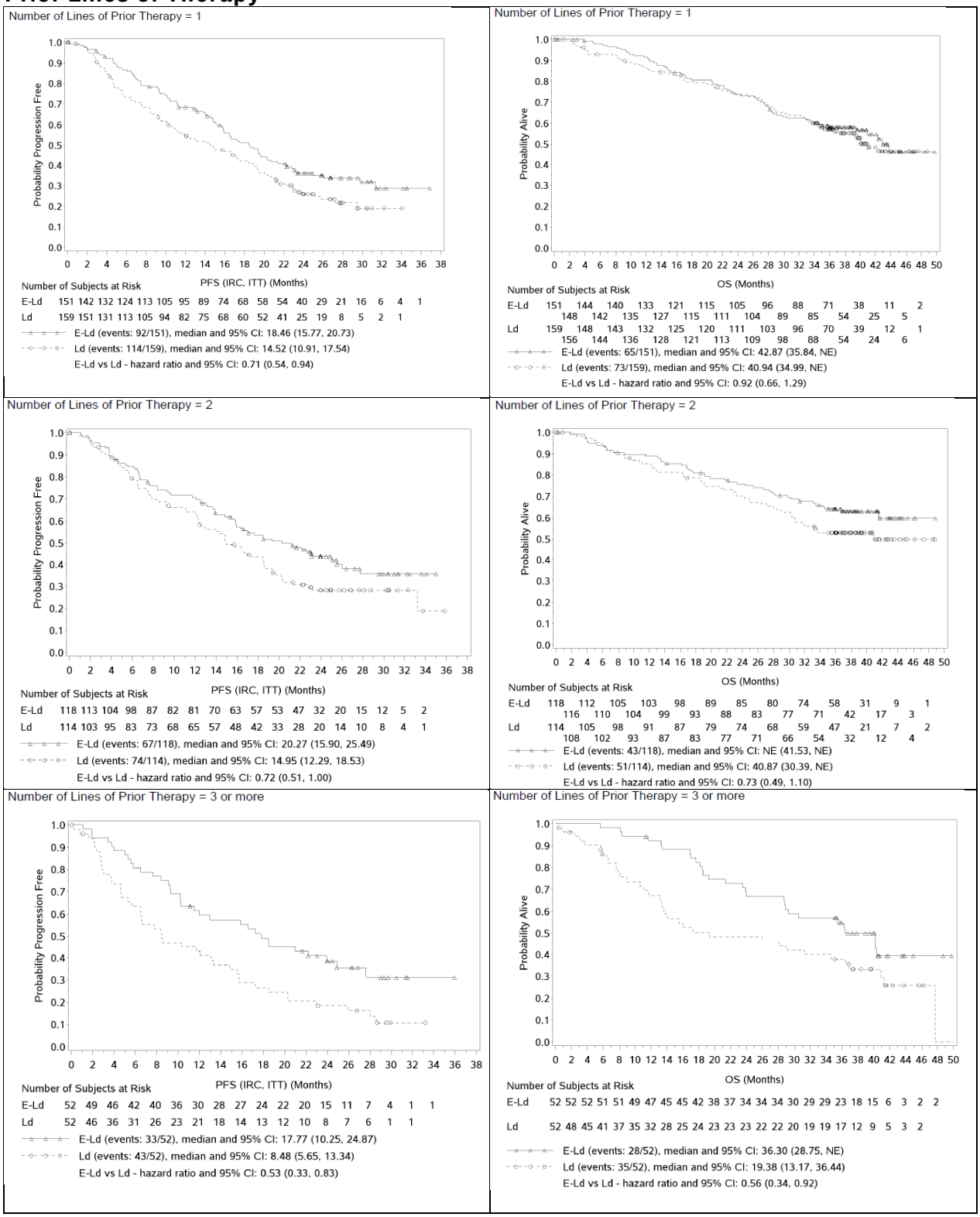
	E-Ld (321)	Ld (325)
Line of therapy		
1	151	159
2	118	114
3	52	52
Prior Systemic Therapy		
Bortezomib	219	231
Cyclophosphamide	154	163
Lenalidomide	16	21
Melphalan	220	197
Thalidomide	153	157
Stem Cell Transplant		
Yes	167	185
No	154	140

Table 13. PFS (IRC, Primary All Randomized Subjects Definition) Hazard Ratio and 95% CI in Subsets ((CA204004)

Subset description	E-Ld N = 321 Median PFS (months) [95% CI]	Ld N = 325 Median PFS (months) [95% CI]	HR [95% CI]
Age			
< 65 years	19.4 [15.9, 23.1]	15.7 [11.2, 18.5]	0.74 [0.55, 1.00]
≥ 65 years	18.5 [15.7, 22.2]	12.9 [10.9, 14.9]	0.64 [0.50, 0.82]
Risk factors			
High risk	14.8 [9.1, 19.6]	7.2 [5.6, 11.2]	0.63 [0.41, 0.95]
Standard risk	19.4 [16.5, 22.7]	16.4 [13.9, 18.5]	0.75 [0.59, 0.94]
Cytogenetic category			
Presence of del17p	19.6 [15.8, NE]	14.9 [10.6, 17.5]	0.65 [0.45, 0.93]
Absence of del17p	18.5 [15.8, 22.1]	13.9 [11.1, 16.4]	0.68 [0.54, 0.86]
Presence of t(4;14)	15.8 [8.4, 18.4]	5.5 [3.1, 10.3]	0.55 [0.32, 0.98]
Absence of t(4;14)	19.6 [17.0, 23.0]	14.9 [12.4, 17.1]	0.68 [0.55, 0.84]
ISS Stage			
I	22.2 [17.8, 31.3]	16.4 [14.5, 18.6]	0.61 [0.45, 0.83]
II	15.9 [9.5, 23.1]	12.9 [11.1, 18.5]	0.83 [0.60, 1.16]
III	14.0 [9.3, 17.3]	7.4 [5.6, 11.7]	0.70 [0.48, 1.04]
Prior therapies			
Lines of prior therapy = 1	18.5 [15.8, 20.7]	14.5 [10.9, 17.5]	0.71 [0.54, 0.94]
Lines of prior therapy = 2 or 3	18.5 [15.9, 23.9]	14.0 [11.1, 15.7]	0.65 [0.50, 0.85]
Prior thalidomide exposure	18.4 [14.1, 23.1]	12.3 [9.3, 14.9]	0.61 [0.46, 0.80]
No prior immunomodulatory exposure	18.9 [15.8, 22.2]	17.5 [13.0, 20.0]	0.78 [0.59, 1.04]
Prior bortezomib exposure	17.8 [15.8, 20.3]	12.3 [10.2, 14.9]	0.67 [0.53, 0.84]
No prior bortezomib exposure	21.4 [16.6, NE]	17.5 [13.1, 21.3]	0.70 [0.48, 1.00]
Response to therapy			
Relapsed	19.4 [16.6, 22.2]	16.6 [13.0, 18.9]	0.75 [0.59, 0.96]
Refractory	16.6 [14.5, 23.3]	10.4 [6.6, 13.3]	0.55 [0.40, 0.76]
Renal function			
Baseline CrCl < 60 mL/min	18.5 [14.8, 23.3]	11.7 [7.5, 17.4]	0.56 [0.39, 0.80]
Baseline CrCl ≥ 60 mL/min	18.5 [15.9, 22.2]	14.9 [12.1, 16.7]	0.72 [0.57, 0.90]

Number of prior lines of therapy

Figure 3. Kaplan-Meier Plot of PFS (IRC, ITT) *(left column)* and of OS by Number of Prior Lines of Therapy



Co-Primary endpoint: ORR

Results in terms of the best overall response and duration (IRC) for all randomized subjects are reported in Table 19.

Table 14. Best Overall Response (IRC) - All Randomized Patients (CA204004)

	E-Ld N = 321		Ld N = 325
BEST OVERALL RESPONSE			
STRINGENT COMPLETE RESPONSE (SCR)	9 (2.8)		5 (1.5)
COMPLETE RESPONSE (CR)	5 (1.6)		19 (5.8)
VERY GOOD PARTIAL RESPONSE (VGPR)	91 (28.3)		67 (20.6)
PARTIAL RESPONSE (PR)	147 (45.8)		122 (37.5)
MINIMAL RESPONSE (MR)	22 (6.9)		33 (10.2)
STABLE DISEASE (SD)	30 (9.3)		54 (16.6)
PROGRESSIVE DISEASE (PD)	8 (2.5)		8 (2.5)
NOT EVALUABLE (NE)	9 (2.8)		17 (5.2)
OBJECTIVE RESPONSE RATE (1) 95% CI FOR OBJECTIVE RESPONSE RATE	252 /321 (78.5%) (73.6, 82.9)		213 /325 (65.5%) (60.1, 70.7)
CMH ESTIMATE OF COMMON ODDS RATIO (2) (3) 95% CI FOR COMMON ODDS RATIO 99.5% CI FOR COMMON ODDS RATIO P-VALUE		1.94 (1.36, 2.77) (1.17, 3.23) 0.0002	
DIFFERENCE IN OBJECTIVE RESPONSE RATE (4) 95% CI FOR DIFFERENCE IN OBJECTIVE RESPONSE RATE		12.6% (6.1, 19.2)	

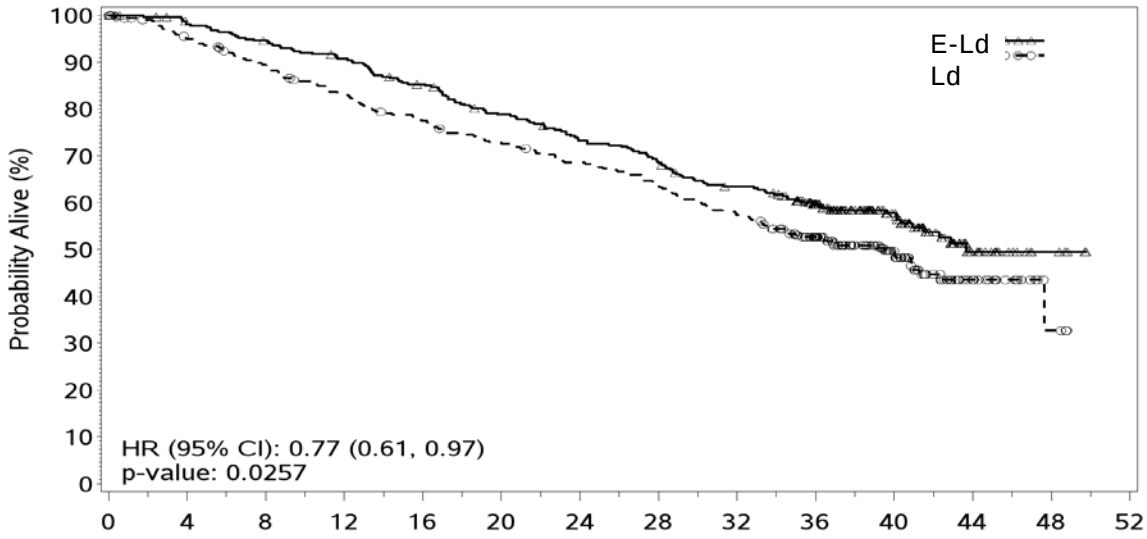
Secondary endpoint: OS

The results of the preliminary (cut-off date of 29 October 2014) and the updated analysis (cut-off date of 29 October 2015; 69% of events) of OS are presented in Table 20 and Figure 6.

Table 15. Preliminary and updated median OS (months 95% CI) and OS rates

	E-Ld	Ld
Median OS months 95% CI		
Preliminary Cut-off 29 October 2014	NE (36.2, NE)	34.6 (29.0, NE) HR: 0.71 (95% CI: 0.54, 0.93)
Update Cut-off 29 October 2015	43.7 (40.3, NE)	39.6 (33.3, NE) HR 0.77 (95% CI: 0.61,0.97)
Overall Survival rate (95% CI)		
Preliminary: **1** year OS rate	91% (87, 93)	83% (78, 87)
Preliminary: **2** year OS rate	74% (69, 79)	68% (63, 73)
Update: **1** year OS rate	91% (87, 93)	83% (78, 87)
Update: **2** year OS rate	73% (68, 78)	69% (63, 73)
Update: **3** year OS rate	60% (54, 65)	53% (47, 58)

Figure 4. Kaplan-Meier Plot of Overall Survival (cut-off date 29 October 2015)– All Randomized Patients (CA204004)



- Overall Survival (Months)
  Number of Subjects at Risk

E-Ld	321	308	296	283	264	242	224	210	191	152	84	23	5
Ld	325	298	278	255	237	222	208	193	174	134	69	22	3

Exploratory endpoints

The median time to first response per IRC was 1.87 months in both treatment groups, and this was comparable to the investigator assessment (1.9 months in both arms). The median time to best response per IRC was 2.8 months for both treatment arms (3.8 months per investigator) (data not shown).

The median duration of response per IRC was 20.7 months in the E-Ld group and 16.6 months in the Ld group (data not shown).

No statistically significant changes from baseline were observed between the treatment groups in terms of the quality of life exploratory endpoints endpoints (Tables 21 and 22).

Table 16. Comparison of Post-Baseline EORTC-QLQ-C30 Scores – All Randomized Patients (CA204004)

Scale	Effect	Estimate	SE	P-value (A)
Functional Scales and Global Health Status Scale				
PHYSICAL FUNCTIONING SCALE	TREATMENT	-1.34	1.1801	0.2570
ROLE FUNCTIONING SCALE	TREATMENT	1.02**	1.6397	0.5323
EMOTIONAL FUNCTIONING SCALE	TREATMENT	-1.02	1.1758	0.3876
COGNITIVE FUNCTIONING SCALE	TREATMENT	0.38**	1.2351	0.7600
SOCIAL FUNCTIONING SCALE	TREATMENT	-0.36	1.4389	0.8048
GLOBAL HEALTH STATUS	TREATMENT	-0.32	1.0891	0.7664
Symptoms Scale				
FATIGUE SCALE	TREATMENT	-0.02**	1.3112	0.9900
NAUSEA AND VOMITING SCALE	TREATMENT	-0.06**	0.6879	0.9338
PAIN SCALE	TREATMENT	-2.50**	1.4373	0.0824
Individual Items				
DYSPNEA	TREATMENT	0.20	1.4206	0.8908
INSOMNIA	TREATMENT	-1.67**	1.4608	0.2541
APPETITE LOSS	TREATMENT	1.59	1.3110	0.2259
CONSTIPATION	TREATMENT	0.28	1.3244	0.8307
DIARRHEA	TREATMENT	-1.21**	1.2082	0.3151
FINANCIAL DIFFICULTIES	TREATMENT	4.37	1.3948	0.0018

(A) P-value from longitudinal model with fixed effects for treatment, time point (categorical), baseline score; and a banded longitudinal covariance matrix.
For the functional scales and Global health status/QoL scale, a higher score represents a better health state. Thus, a positive change from baseline would indicate a better QoL. For the symptom scales and individual items, a lower score represents a better health state. Thus, a negative change from baseline would indicate a better QoL.
** indicates that treatment effect is in favor of elotuzumab.

Table 17. Comparison of Post-Baseline EORTC-QLQ-MY20 Scores – All Randomized Patients (CA204004)

Scale	Effect	Estimate	SE	P-value (A)
DISEASE SYMPTOM SCALE	TREATMENT	-0.95**	1.0730	0.3770
SIDE EFFECT OF TREATMENT	TREATMENT	-0.15**	0.7698	0.8465
FUTURE PERSPECTIVE SCALE	TREATMENT	0.00**	1.3125	0.9970
BODY IMAGE SCALE	TREATMENT	1.09**	1.5752	0.4875

(A) P-value from longitudinal model with fixed effects for treatment, time point (categorical), baseline score; and a banded longitudinal covariance matrix.
For the disease symptoms and side effects scales, a high score represents a high level of symptomatology or problems (worse QoL), whilst for the future perspective and body image scales, a high score represents a high level of functioning (better QoL).
** indicates that treatment effect is in favor of elotuzumab.

Ancillary analyses

Time to next therapy (TTNT)

In study CA204004, subjects who discontinued therapy were followed for PFS and/or OS. As part of this assessment, the subsequent systemic therapy for treating MM was collected. Time to next therapy defined as the time from randomization to earliest start date of subsequent myeloma systemic therapy. Based on these results, the HR for TTNT is 0.62 (CI: 0.49, 0.78). KM curves for TTNT early diverged and further separated after approximately 1 year (median TTNT is NE with E-Ld [95%CI 28.3, NE] and 21.22 months with Ld [95%CI 18.07; 23.20]).

Summary of main study

The following tables summarises the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 18. Summary of efficacy for trial CA204004

Title: A phase 3, randomized, open-label trial of lenalidomide/dexamethasone (ld) with or without elotuzumab in relapsed or refractory multiple myeloma.			
Study identifier	CA204004		
Design	Phase 3, Randomized, Open-Label		
	Study initiation date: Study completion date:		14 June 2011 1 September 2014
Hypothesis	Superiority		
Treatments groups	Elotuzumab + Ld (n=321)		Elotuzumab: 10 mg/kg IV in 4-week cycles, every week for 2 cycles and every 2 weeks thereafter. Lenalidomide: 25 mg PO daily first 3 weeks of each cycle Dexamethasone: 40 mg PO weekly in weeks without elotuzumab, or 28 mg PO + 8 mg IV in weeks with elotuzumab.
	Ld (n=325)		Lenalidomide: 25 mg PO daily first 3 weeks of each cycle Dexamethasone: 40 mg PO weekly
Endpoints and definitions	Co-Primary endpoint	Progression Free Survival (PFS)	Time from randomization to the date of the first documented tumour progression per IRC or death
	Co-Primary Endpoint	Overall Response Rate (ORR)	Proportion of randomized patients who have either partial response or complete response per IRC.
	Secondary endpoints	Overall Survival (OS)	Time from randomization to the date of death from any cause.
Clinical database lock	4 November 2014		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Randomized patients (N=646)		
Descriptive statistics and estimate variability	Treatment group	E-Ld	Ld
	Number of subject	321	325
	Median PFS (months)	18.5	14.3
	95% CI	16.5, 21.4	12.0, 16.0
	ORR N (%)	252 (78.5)	213 (65.5)
	95% CI	73.6, 82.9	60.1, 70.7
	Median OS (months) 95% CI	NE 36.2, NE	34.6 months 29.0, NE
	PFS	Comparison groups	E-Ld vs Ld
		Hazard Ratio (HR)	0.68

		95% CI	0.55, 0.85
		P-value	0.0001
	ORR	Comparison groups	E-Ld vs Ld
		Common Odds Ratio	1.94
		95% CI	1.36, 2.77
		P-value	0.0002
	OS	Comparison groups	E-Ld vs Ld
		Hazard Ratio (HR)	0.77
		95% CI	0.61, 0.97
		P-value	0.0257
Notes	Randomization was stratified by:β2 microglobulin (< 3.5 versus ≥ 3.5 mg/L); Number of prior lines of therapy (1 versus 2 or 3); Prior IMiD (no vs prior thalidomide only vs other)		

Study CA204009

This was a Phase 2, randomized trial investigating the combination of Elotuzumab with bortezomib and dexamethasone (E-Bd) versus bortezomib and dexamethasone alone (Bd) in subjects with relapsed/refractory multiple myeloma.

Methods

Study Participants

Key inclusion criteria

- ≥ 18 years of age
- Eastern Cooperative Oncology group (ECOG) performance status ≤2
- Confirmed diagnosis of MM with documented progression by modified IMWG criteria after or during the most recent therapy; AND
- Measurable disease as defined by at least 1 of the following:
    - Serum IgG, IgA or IgM M-protein ≥0.5 g/dL or serum IgD M-protein ≥0.05 g/dL OR
    - Urine M-protein ≥ 200 mg excreted in a 24-hour collection sample
    - Involved serum free light chain level ≥10 mg/dL, provided the free light chain ratio is abnormal
- Proteasome inhibitor naïve or prior proteasome inhibitor exposure was permitted provided all of the following criteria were met:
    - Best achieved response was ≥ PR to previous proteasome inhibitor
    - Patient did not discontinue any proteasome inhibitor due to intolerance or grade ≥ 3 toxicity
    - Patient was not refractory to any proteasome inhibitor (defined as progression during treatment or within 60 days after the last dose)

Key exclusion criteria

- Solitary bone or solitary extramedullary plasmacytoma as the only evidence of plasma cell dyscrasia
- MGUS, smoldering myeloma or Waldenström's macroglobulinemia
- Active plasma cell leukemia
- Primary refractory disease (best response of SD with all prior therapies)
- Thalidomide, lenalidomide, or cytotoxic chemotherapy within 2 weeks of first dose of study drugs
- Major surgery within 4 weeks prior to randomization
- Prior autologous stem cell transplant within 12 weeks, or allogeneic stem cell transplant within 16 weeks of the first dose of drug
- Any medical conditions that, in the investigator's opinion, would impose excessive risk to the patient. Examples of such conditions include: any uncontrolled disease, any altered mental status that would interfere with the understanding of the informed consent.
- Significant cardiac disease
- Prior or concurrent malignancy, except for adequeately treated basal cell or squamous cell skin cancer or any other cancer from which the patient has been disease-free for >3 years.
- Grade 1 neuropathy with pain or any ≥ Grade 2 neuropathy
- Any residual AEs from prior chemotherapy, surgery or radiotherapy that have not resolved to < Grade 2
- Laboratory test findings:
    - Corrected serum calcium ≥ 11.5 mg/dL
    - Absolute neutrophil count < 1000 cells/mm3. No G-CSF or GM-CSF allowed within 1 week of randomization
    - Platelets < 75,000 cell/mm^3 (75 x 10^9/L)
    - Haemoglobin < 8 g/dL
    - Creatinine clearance < 30 mL/minute measured by 24-hour urine collection or estimated by the Cockcroft-Gault formula
    - Total bilirubin > 1.5 x upper limit of normal (ULN)
    - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥3 x ULN

Treatments

Patients were treated with elotzumab + Bd or Bd alone. The treatment schedule is presented in Table 24.

Table 19. Treatment Schedule (Study CA204009)

Cycles 1 and 2 with 21-day cycles										
Day	**1**	**2**	**4**	**5**	**8**	**9**	**11**	**12**	**15**	**16**
Bortezomib	X		X		X		X			
Dexamethasone[a]	X	X	X	X	X	X	X	X[b]	X[c]	
Elotuzumab[d]	X				X				X	
Cycles 3 through 8 with 21-day cycles										
Day	**1**	**2**	**4**	**5**	**8**	**9**	**11**	**12**	**15**	**16**
Bortezomib	X		X		X		X			
Dexamethasone[a]	X	X	X	X	X	X	X	X		
Elotuzumab[d]	X						X			
Cycles 9+ with 28-day cycles										
Day	**1**	**2**	**4**	**5**	**8**	**9**	**11**	**12**	**15**	**16**
Bortezomib	X				X				X	
Dexamethasone[a]	X	X			X	X			X	X
Elotuzumab[d]	X								X	

Source: Appendix 1.1

[a] Dexamethasone dosing:
- On days when elotuzumab is administered (Investigational Arm only):
  - Dexamethasone 8 mg po (3 to 24 hours prior to start of elotuzumab infusion) AND
  - Dexamethasone 8 mg IV (at least 45 minutes prior to start of elotuzumab infusion).
- On days when elotuzumab is NOT administered:
  - Dexamethasone 20 mg po

[b] control arm only

[c] investigational arm only

[d] Elotuzumab in investigational arm only

Elotuzumab was administered weekly at a dose of 10 mg/kg IV. Dose reductions were not permitted. In cycle 3 and beyond, elotuzumab dosing could be delayed by up to 1 week as clinically indicated.

Bortezomib was administered at a dose of 1.3 mg/m^2 as IV bolus or SQ injection. The treatment schedule is different between cycles (Table 18).

Dexamethasone was administered at a dose of 20 mg p.o on days without elotuzumab infusion. On days of elotuzumab infusion, dexamethasone was administered at a split dose of 8 mg p.o (3-24 hours before the start of infusion), and 8 mg IV (at least 45 minutes prior to elotuzumab infusion).

Co-medication included:

- Oral anti-viral therapy (acyclovir or equivalent)
- Patients were required to receive pre-medication 30-90 minutes prior to each dose of elotuzumab:
  - H1 blocker: diphenhydramine (25-50 mg PO or IV) or equivalent
  - H2 blocker: ranitidine (50 mg IV) or equivalent
  - Acetaminophen (650-1000 mg PO)

Treatment with study drug continued until disease progression or unacceptable toxicity.

Objectives

The primary objective was to compare the progression free survival (PFS) of E-Bd versus Bd alone.

Secondary objectives included the comparison of response rates between arms in the overall population and between arms in the subgroup of subjects with at least one FcγRIIIa V allele. Estimation of the PFS hazard ratio in the subgroup of subjects with at least one FcγRIIIa V allele was also a secondary objective.

Exploratory objectives included the evaluation of: safety of elotuzumab in combination with bortezomib and dexamethasone, to estimate PFS HR and difference in response rates between arms in the subgroup of subjects with no FcγRIIIa V allele; to estimate overall survival, time to tumour response (TTR) and duration of response (DOR) in the overall population and the FcγRIIIa V allele subgroups; to estimate the interaction between treatment and the presence of at least one FcγRIIIa V allele on PFS; to characterise PK of elotuzumab and explore exposure-response relationships with respect to safety, efficacy, and biomarkers; to identify and evaluate potential pharmacodynamic and/or predictive biomarkers of activity of elotuzumab in combination with bortezomib and dexamethasone; to evaluate immunogenicity of elotuzumab.

Outcomes/endpoints

The primary endpoint was PFS defined as PFS is the time from randomization to the date of the first documented tumour progression or death due to any cause.

The secondary endpoints was ORR defined as the proportion of randomized subjects who achieve a best response of complete response (CR), stringent complete response (sCR), very good partial response (VGPR), or partial response (PR) using the modified IMWG criteria as per investigator's assessment).

Exploratory endpoints included TTR (defined as the time from randomization to the first objective documentation of PR or better), DOR (time that the criteria for objective response are first met until the date of a progression event), OS (time from randomization to the date of death from any cause).

Sample size

The planned sample size was 150 patients. The comparison of PFS between treatment arms was planned to be made at the one-sided, 0.15, significance level because this is a proof-of-concept trial, rather than a confirmatory trial. The study would require at least 103 progression events (documented progressions or deaths) to complete. This number of events ensured that a one-sided, 0.15 level log-rank test will have 80% power if the median PFS times in the control and investigational arms are 10 months and 14.5 months, respectively, ie, if the hazard ratio of the investigational arm to the control arm is 0.69. Assuming an accrual rate of 10 subjects per month, the study would take approximately 28 months for final PFS evaluation.

Randomisation

Patients were randomized to receive either elotzumab + Bd or Bd with a ratio of 1:1 and stratified based on: Prior proteasome inhibitor exposure (yes vs. no); Presence of at least one FcγRIIIa V allele (yes vs. no) and Number of prior lines of therapy (1 vs. 2 or 3).

Blinding (masking)

This was an open-label study.

Statistical methods

Efficacy analyses (PFS, ORR and OS) were conducted on the population of all randomized subjects (all subjects who gave signed informed consent and who were entered in the IVRS).

The Kaplan-Meier (KM) product limit method was used to estimate the distribution and median of each time-to-event endpoint in which censoring is involved. Breslow method was used for handling ties. The

median along with CIs were estimated based on Brookmeyer and Crowley methodology (using log-log transformation for constructing the CIs). A stratified (by IVRS stratification factors and treatment as the sole covariate) Cox proportional hazards model was used to compute an estimate and CI for the hazard ratio of E-Bd to Bd. Rates at fixed time points (i.e. PFS at 1 year) were derived from the K-M estimate along with their corresponding log-log transformed 95% CIs.

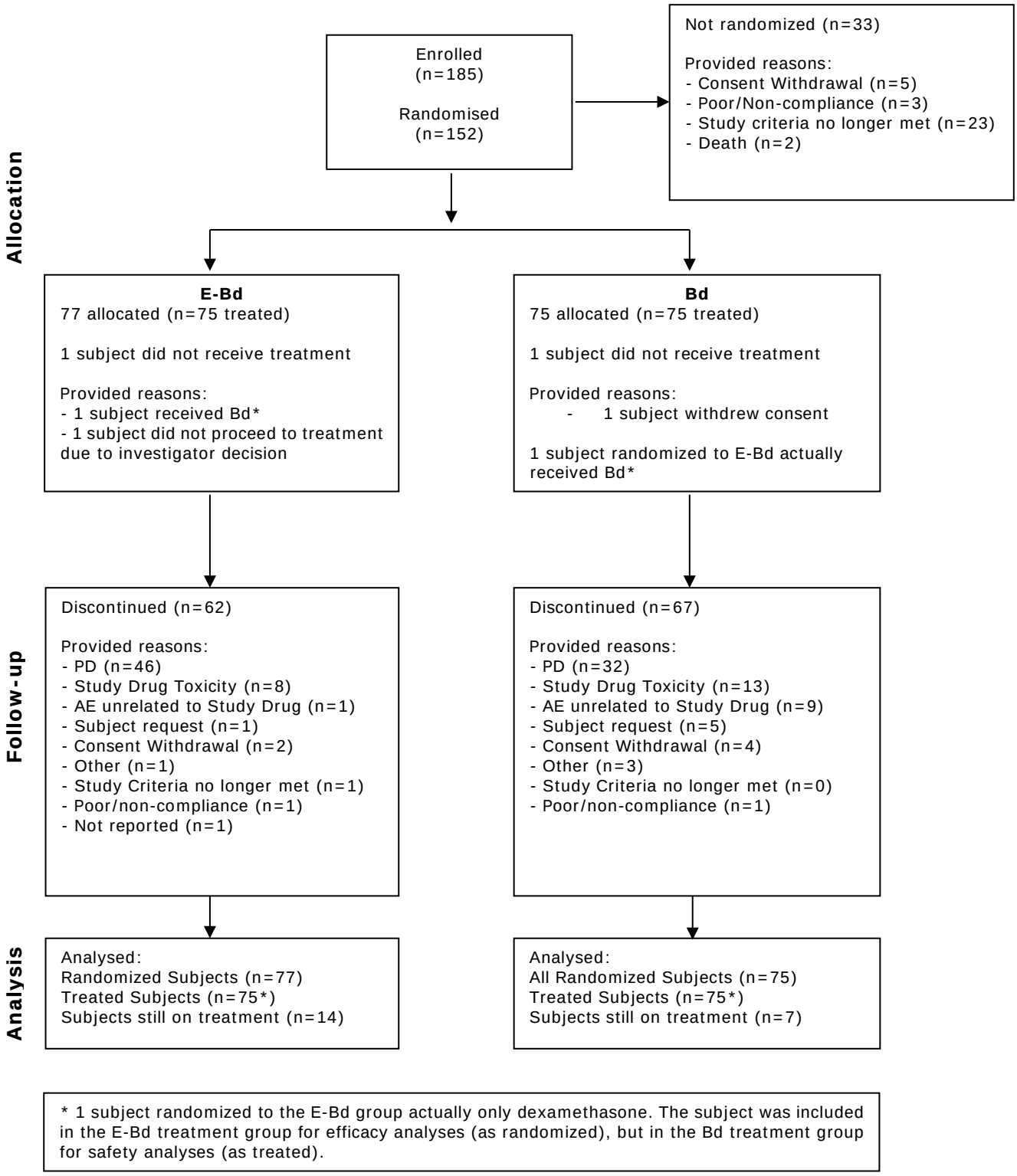
An analysis of PFS was also performed using an unstratified multivariate Cox regression model to estimate the treatment effect after adjustment for possible imbalances in pre-specified potential prognostic factors. This model consisted of the following baseline covariates, in addition to the treatment arm as randomized: prior proteasome use (yes versus no); presence of at least one FcγRIIIa V allele (yes versus no); number of prior lines of therapy (1 versus 2 or 3); age (<65 versus ≥ 65 years); ECOG PS (0-1 versus 2); Prior stem cell transplantation (yes versus no); Best response to last therapy (PR or better versus minimal response or below); Creatinine clearance (< 60 ml/min vs ≥60 ml/min); LDH (<300 IU/L, ≥300 IU/L). The influence of baseline and demographic characteristics on the treatment effect on the PFS by primary definition was explored via subset analyses. In order to summarize the PFS distribution in each arm in each of the subsets, there should have been at least 10% (ie, 12 PFS events) of the events in each level of the subset.

The level of the covariate normally associated with the worst prognosis was coded as the reference level. All the specified analyses of PFS were repeated using the secondary definitions of ATA.

Beyond the analyses in the overall study population, subset analyses of PFS and ORR were also performed by baseline and demographic characteristics.

Results

Participant flow



Recruitment

Patients were enrolled from 31 January 2012 through 15 April 2013. The last patient visit (for the primary endpoint) was on 30 May 2014. Subjects were enrolled at 53 sites in 4 countries. Subjects were accrued from France (13.8%), Italy (43.4%), Spain (11.2%) and the United Sates (31.6%).

Conduct of the study

Study protocol amendments

The original study protocol was dated 20 July 2011 and was subsequently amended 2 times. The major changes were as follows:

Protocol amendment 20 April 2012

- Addition of entry criterion to exclude patients previously exposed to elotuzumab
- Response Criteria Modified from IMWG was revised to agree with criteria appropriate for use with the study population
- Additional clarification provided on the objectives of the second interim analysis, to not only evaluate safety, but also look at preliminary efficacy data in order to make early program level decisions.

Protocol amendment 25 October 2012

- Modifications to the inclusion criteria include
    - broadening the number of lines of prior therapy from 1 - 2 lines to 1 – 3 lines of therapy and
    - Allowing up to 15% of patients to have had prior non-bortezomib proteasome inhibitor therapy
- Broadening of the stratification criteria to adapt to these changes, ie, stratification of subjects during randomization will be based on subjects have 1 versus 2 or 3 lines of therapy, instead of 1 versus 2 lines of therapy, and subjects being proteasome inhibitor naive versus having had prior proteasome inhibitor exposure, instead of bortezomib naive versus prior bortezomib exposure
- Removal of the exclusion criteria describing subjects with uncontrolled diabetes defined as an HbA1c ≥ 8.0 and decreasing the disease-free interval for subjects with other prior malignancy from 5 years to 3 years
- Clarification that once subjects reach cycle 5 without any Grade ≥2 infusion reactions, the infusion rate at C5D1 should be increased by 1 mL per minute in a stepwise fashion in each cycle up to a maximum of 5 mL per minute.

Protocol compliance

Relevant protocol deviations were defined as a deviation from the protocol which could be programmed using the database and which could potentially affect the interpretability of the study results. In the E-Bd arm 4 patients had at least one relevant protocol deviation, in the Bd arm 8 patients. The type of protocol deviations was equally divided in both arms: half of the deviations were caused by eligibility deviations (non-measurable disease) and half of the deviations were on-treatment (continuous study therapy 4 weeks after progression per investigator, i.e. 8 weeks after first date of documented progression).

Baseline data

Demographic and baseline characteristics are shown in Table 25 and in Table 26, respectively.

Table 20. Demographic Characteristics – All Treated Patients (Study CA204009)

	E-Bd N = 77	Bd N = 75	Total N = 152
AGE (YEARS)			
N	77	75	152
MEAN	65.4	65.1	65.3
MEDIAN	66.0	66.0	66.0
MIN , MAX	25 , 82	30 , 85	25 , 85
Q1 , Q3	61.0 , 72.0	58.0 , 73.0	59.5 , 72.5
STANDARD DEVIATION	9.48	10.34	9.88
AGE CATEGORIZATION (%)			
< 65	34 (44.2)	33 (44.0)	67 (44.1)
>= 65 AND < 75	28 (36.4)	28 (37.3)	56 (36.8)
>= 75	15 (19.5)	14 (18.7)	29 (19.1)
GENDER (%)			
MALE	42 (54.5)	37 (49.3)	79 (52.0)
FEMALE	35 (45.5)	38 (50.7)	73 (48.0)
RACE (%)			
WHITE	68 (88.3)	65 (86.7)	133 (87.5)
BLACK OR AFRICAN AMERICAN	4 (5.2)	7 (9.3)	11 (7.2)
AMERICAN INDIAN OR ALASKA NATIVE	0	0	0
ASIAN	0	1 (1.3)	1 (0.7)
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	1 (1.3)	0	1 (0.7)
OTHER	3 (3.9)	2 (2.7)	5 (3.3)
NOT REPORTED	1 (1.3)	0	1 (0.7)
ETHNICITY (%)			
HISPANIC OR LATINO	7 (9.1)	4 (5.3)	11 (7.2)
NOT HISPANIC OR LATINO	44 (57.1)	47 (62.7)	91 (59.9)
NOT REPORTED	26 (33.8)	24 (32.0)	50 (32.9)

Table 21. Baseline Disease Characteristics – All Randomized Patients (Study CA204009)

	E-Bd N = 77	Bd N = 75	Total N = 152
M-PROTEIN, SERUM (QUANTITATIVE SPE) (G/L)			
N	77	74	151
MEAN	23.2	22.1	22.6
MEDIAN	22.0	20.0	21.0
MIN , MAX	0 , 91	0 , 73	0 , 91
Q1 , Q3	7.0 , 33.0	7.0 , 31.0	7.0 , 33.0
STANDARD DEVIATION	19.51	16.97	18.26
M-PROTEIN, URINE (G/DAY)			
N	60	58	118
MEAN	0.348	1.259	0.795
MEDIAN	0.000	0.000	0.000
MIN , MAX	0.00 , 6.70	0.00 , 39.60	0.00 , 39.60
Q1 , Q3	0.000 , 0.180	0.000 , 0.510	0.000 , 0.410
STANDARD DEVIATION	1.0337	5.3000	3.7991
NUMBER OF LYTIC BONE LESIONS			
0	30 (39.0)	32 (42.7)	62 (40.8)
1 - 3	11 (14.3)	12 (16.0)	23 (15.1)
> 3	31 (40.3)	24 (32.0)	55 (36.2)
NOT REPORTED	5 (6.5)	7 (9.3)	12 (7.9)
PLASMACYTOMA			
YES	5 (6.5)	6 (8.0)	11 (7.2)
NO	7 (9.1)	12 (16.0)	19 (12.5)
UNKNOWN	1 (1.3)	1 (1.3)	2 (1.3)
NOT REPORTED	64 (83.1)	56 (74.7)	120 (78.9)

MYELOMA TYPE			
IGG	43 (55.8)	40 (53.3)	83 (54.6)
IGA	16 (20.8)	13 (17.3)	29 (19.1)
IGM	0	1 (1.3)	1 (0.7)
IGD	0	2 (2.7)	2 (1.3)
LIGHT CHAIN ONLY	6 (7.8)	5 (6.7)	11 (7.2)
BICLONAL	1 (1.3)	0	1 (0.7)
TRICLONAL	0	3 (4.0)	3 (2.0)
NOT CLASSIFIED	3 (3.9)	1 (1.3)	4 (2.6)
NOT REPORTED	8 (10.4)	10 (13.3)	18 (11.8)
ISS STAGE			
STAGE I	26 (33.8)	19 (25.3)	45 (29.6)
STAGE II	23 (29.9)	20 (26.7)	43 (28.3)
STAGE III	11 (14.3)	16 (21.3)	27 (17.8)
NOT REPORTED	17 (22.1)	20 (26.7)	37 (24.3)
RISK CATEGORY			
HIGH RISK	0	5 (6.7)	5 (3.3)
LOW RISK	0	3 (4.0)	3 (2.0)
STANDARD RISK	36 (46.8)	25 (33.3)	61 (40.1)
NOT EVALUABLE	41 (53.2)	42 (56.0)	83 (54.6)

Table 22. Previous Anti-Cancer Regimens

	E-Bd N = 77	Bd N = 75	Total N = 152
NUMBER OF SUBJECTS WITH AT LEAST ONE PRIOR SYSTEMIC THERAPY	77 (100.0)	75 (100.0)	152 (100.0)
NUMBER OF REGIMENS			
MEDIAN	1.0	1.0	1.0
MIN , MAX	1 , 3	1 , 3	1 , 3
NUMBER OF REGIMENS			
1	50 (64.9)	51 (68.0)	101 (66.4)
2	25 (32.5)	18 (24.0)	43 (28.3)
3	2 (2.6)	6 (8.0)	8 (5.3)
PRIOR THERAPY			
STEM CELL TRANSPLANT	39 (50.6)	41 (54.7)	80 (52.6)
RADIOTHERAPY	16 (20.8)	13 (17.3)	29 (19.1)
SURGERY	12 (15.6)	9 (12.0)	21 (13.8)
REGIMEN			
DEXAMETHASONE/LENALIDOMIDE	17 (22.1)	15 (20.0)	32 (21.1)
BORTEZOMIB/DEXAMETHASONE	11 (14.3)	4 (5.3)	15 (9.9)
DEXAMETHASONE/THALIDOMIDE	5 (6.5)	5 (6.7)	10 (6.6)
BORTEZOMIB/MELPHALAN/PREDNISONE	4 (5.2)	5 (6.7)	9 (5.9)
BORTEZOMIB/DEXAMETHASONE/LENALIDOMIDE	3 (3.9)	5 (6.7)	8 (5.3)
MELPHALAN/PREDNISONE/THALIDOMIDE	4 (5.2)	4 (5.3)	8 (5.3)
OTHER	49 (63.6)	54 (72.0)	103 (67.8)
DRUGS			
ANTINEOPLASTIC & IMMUNOMODULATING AGENT	73 (94.8)	73 (97.3)	146 (96.1)
ANTINEOPLASTIC AGENTS	62 (80.5)	65 (86.7)	127 (83.6)
BORTEZOMIB	38 (49.4)	40 (53.3)	78 (51.3)
MELPHALAN	32 (41.6)	37 (49.3)	69 (45.4)
CYCLOPHOSPHAMIDE	21 (27.3)	20 (26.7)	41 (27.0)
DOXORUBICIN	12 (15.6)	9 (12.0)	21 (13.8)
VINCRISTINE	9 (11.7)	6 (8.0)	15 (9.9)
CARMUSTINE	3 (3.9)	1 (1.3)	4 (2.6)
DOXORUBICIN LIPOSOMAL	2 (2.6)	1 (1.3)	3 (2.0)
ETOPOSIDE	2 (2.6)	1 (1.3)	3 (2.0)
CISPLATIN	1 (1.3)	1 (1.3)	2 (1.3)
BENDAMUSTINE	0	1 (1.3)	1 (0.7)
BUSULFAN	0	1 (1.3)	1 (0.7)
CARFILZOMIB	1 (1.3)	0	1 (0.7)
EPIRUBICIN	1 (1.3)	0	1 (0.7)
IFOSFAMIDE	1 (1.3)	0	1 (0.7)
INVESTIGATIONAL ANTINEOPLASTIC	0	1 (1.3)	1 (0.7)
IMMUNOSUPPRESSIVE AGENT	38 (49.4)	41 (54.7)	79 (52.0)
LENALIDOMIDE	38 (49.4)	41 (54.7)	79 (52.0)
POMALIDOMIDE	1 (1.3)	0	1 (0.7)

Numbers analyses

The analysis populations of Study CA204009 are summarized in Table 28.

Table 23. Analyses populations (Study CA204009)

Datasets	E-Bd, N	Bd, N	Total
Enrolled: all subjects who signed the informed consent and who were entered in the IVRS	-	-	185
Randomized: all enrolled subjects who were randomized	77[a]	75[a]	152
Treated: all randomized subjects who received at least one dose of study drug (bortezomib, dexamethasone, or elotuzumab)	75[a]	75[a]	150
PK-evaluable: all subjects with at least one dose of elotuzumab and at least one available serum elotuzumab concentration value	75	NA	75

Outcomes and estimation

Primary endpoint: PFS

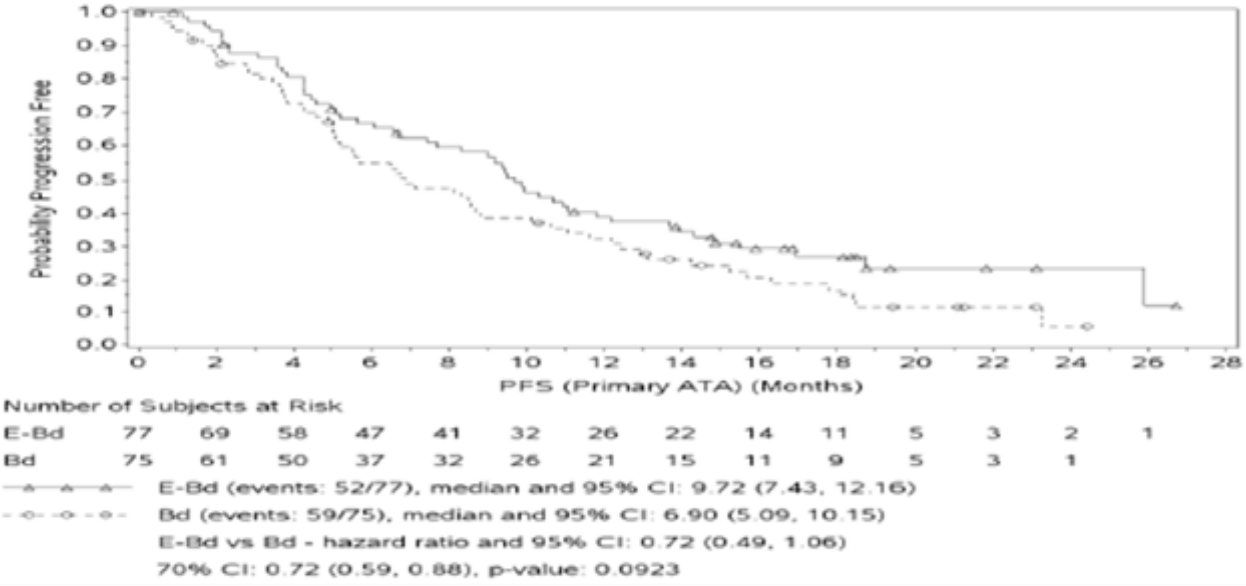
Results in terms of Progressive-Free Survival analysis based on primary adequate tumour assessment (ATA) definition are reported in Table 29 and in Figure 7.

Table 24. Summary of PFS Results Based on Primary definition - ITT, All Randomized Subjects (Study CA204009)

	E-Bd N=77	Bd N=75	Hazard Ratio (E-Bd/Bd)
PFS, months (95% CI)	Events: 52 Censored: 25 Median: 9.72 (7.43, 12.16)	Events:59 Censored:16 Median: 6.90 (5.09, 10.15)	Stratified Cox Model 0.72 70% CI: (0.59, 0.88) 95% CI: (0.49, 1.06) Unstratified Cox Model 0.71 70% CI: (0.58, 0.86) 95% CI: (0.49, 1.03)
1 Year PFS Rate (95% CI)	0.39 (0.28, 0.50)	0.33 (0.22, 0.44)	
Sensitivity Analysis			Multivariate Cox Model[a] 0.53 70% CI: (0.42, 0.66) 95% CI: (0.34, 0.81) p-value = 0.0039 (2-sided)
	Stratified log-rank p-value = 0.0923 (2-sided)		p-value = 0.0039 (2-sided)

a This model consists of the following baseline covariates, in addition to the treatment arm as randomized: prior proteasome use (yes *vs.* no), at least one FcγRIIIa V allele (yes vs. no), number or prior lines of therapy (1 vs. 2 *vs.* 3), age (< 65 *vs.* ≥65 years), ECOG PS (0-1 or 2), prior stem cell transplantation (yes *vs.* no), best response to last therapy (PR or better vs. minimal response or below), creatinine clearance (<60 ml/min *vs.* ≥60 ml/min), and LDH (< 300 IU/L *vs.* ≥300 IU/L).

Figure 5. Kaplan-Meier Plot of primary PFS (Primary ATA) – All Randomized Patients (Study CA204009)



Supportive PFS analyses

In the secondary PFS analysis based on primary ATA definition, the median PFS was 9.7 months in the E-Bd arm (95% CI: 6.57, 15.51), compared to 6.6 months in the Bd arm (95% CI: 5.03, 8.84). The HR was 0.66 (96% CI 0.42, 1.03; 70% CI: 0.52, 0.83; p=0.0645) (data not shown).

Sensitivity analysis PFS

A sensitivity analysis using a multivariate Cox model, adjusting for possible imbalances in pre- specified prognostic factors, yielded an estimated PFS HR of 0.53 (95% CI: 0.34, 0.81; p=0.0039). Only one factor, baseline LDH, significantly influenced PFS, with a PFS HR (LDH < 300 U/L compared to LDH ≥300 U/L) of 0.42 (0.27, 0.65; p=0.0001) (data not shown).

Secondary endpoint

Objective response rate

Best overall response (BOR) in the E-BD arm was 64.9% (95% CI: 53.2, 75.5) compared to 62.7% (95% CI: 50.7, 73.6) in the Bd arm. The 95% CI for the difference in ORR (-13.2, 17.8) included 0, indicating there was no significant difference between the two arms.

For E-Bd and Bd, respectively, 31.2% and 36.0% of patients achieved a PR, 29.9% and 22.7% of patients achieved a VGPR, 3.9% and 2.7% of patients achieved a CR, and 0 and 1.3% of patients achieved a sCR.

There was no difference between treatment groups in BOR for patients with or without at least 1 FcγRIIIα V allele, or other subsets of patients (data not shown).

Exploratory endpoints

Time to tumour response

The median time to response was 1.43 months for the 50 responder patients in the E-Bd arm compared to 1.51 months for the 47 responder patients in the Bd arm.

For patients with at least one FcγRIIIa V allele the median time to tumour response was 1.35 months in the E-Bd arm compared to 1.45 months in the Bd arm (33 responder patients in each arm). For patients without at least one FcγRIIIa V allele, the median duration of response was 1.45 months in the E-BD arm (17 responder patients) compared to 2.18 months in the Bd arm (14 responder patients) (data not shown).

Duration of response

The median duration of response was 10.35 months (95% CI: 8.54, 14.75) in the E-Bd arm compared to 9.26 months in the Bd arm (95% CI: 5.59, 11.73).

For patients with at least one FcγRIIIa V allele the median duration of response was 11.37 months in the E-Bd arm compared to 10.35 months in the Bd arm. For patients without at least one FcγRIIIa V allele, the median duration of response was 9.41 months in the E-BD arm compared to 6.21 months in the Bd arm (data not shown).

Overall survival

Preliminary OS data were provided with 40 reported deaths (17 patients (22.1%) on E-Bd, and 23 patients (30.7%) on Bd) and a median follow up of approximately 18 months in both arms. The 1-year OS rate (95% CI) was 0.85 (0.75, 0.92) for the E-Bd group and 0.74 (0.62, 0.83) for the Bd group.

At 28 months of follow-up, deaths in the empliciti combination with bortezomib and dexamethasone study arm and the bortezomib and dexamethasone study arm were 28 [36%]) and 32 [43%], respectively (data not shown).

Ancillary analyses

N/A

Summary of main study

The following table summarises the efficacy results from Studt CA204009. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 25. Summary of efficacy for trial CA204009

Title: A phase 2, randomized study of bortezomib/dexamethasone with or without elotuzumab in patients with relapsed/refractory multiple myeloma.		
Study identifier	CA204009	
Design	Phase 2, Randomized, Open label	
	Study initiation date	31 Jan 2012
	Study completion date	Follow-up ongoing
Hypothesis	Superiority	
Treatments groups	Elotuzumab + Bd (n=77)	Elotuzumab: 10 mg/kg IV on days 1, 5 and 15 in first 2 (21-day) cycles, on days 1 and 11 of (21-day) cycles 3-8, and every 2 weeks on days 1 and 15 for (28-day) cycles 9 and up. Bortezomib: 1.3 mg/m^2 as IV bolus or SQ injection on days 1, 4, 8 and 11 for 8 (21-day) cycles, on days 1, 8 and 15 for (28-day) cycles 9 and up. Dexamethasone: 20 mg PO daily on days without elotuzumab, or 8 mg PO + 8 mg IV on days with elotuzumab.

	Bd (n=75)		Bortezomib: 1.3 mg/m^2 as IV bolus or SQ injection on days 1, 4, 8 and 11 for 8 (21-day) cycles, on days 1, 8 and 15 for (28-day) cycles 9 and up. Dexamethasone: 20 mg PO daily.
Endpoints and definitions	Primary endpoint	Progression Free Survival (PFS)	Time from randomization to the date of the first documented tumour progression or death due to any cause.
	Secondary endpoint	Objective Response Rate (ORR)	Proportion of randomized subjects who achieve a best response of CR, sCR, VGPR or PR, using the modified IMWG criteria as per investigator's assessment.
	Exploratory endpoint	Overall Survival (OS)	Time from randomization to the date of death from any cause.
Data cut-off	30 May 2014		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Randomized patient population: 152 patients		
Descriptive statistics and estimate variability	Treatment group	E-Bd	Bd
	Number of subject	77	75
	Median PFS (months)	9.7	6.9
	95% CI	7.4, 12.2	5.1, 10.2
	ORR	64.9%	62.7%
	95% CI	53.2, 75.5	50.7, 73.6
	Median OS (months) 95% CI	NE 23.56, NE	26.09 NE, NE

Effect estimate per comparison	PFS	Comparison groups	E-Bd vs Bd
		Hazard Ratio (HR)	0.72
		70% CI	0.59, 0.88
		P-value	0.0923
	ORR	Comparison groups	E-Bd vs Bd
		Difference	2.3
		95% CI	-13.2,17.8
		P-value	-
	Preliminary OS	Comparison groups	E-Bd vs Bd
		Hazard Ratio (HR)	0.61
		95% CI	0.32, 1.15
		P-value	-

Analysis performed across trials (pooled analyses and meta-analysis)

N/A

Clinical studies in special populations

Table 26. Special Age Populations Treated in Elotuzumab Controlled Clinical Studies (Pooled total number: 450/785)

Clinical studies in special populations	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
Controlled studies (Pooled, CA204004 + CA204009)	Total: 296/785	Total: 148/785	Total: 6/785
CA204004 Phase 3, Randomized, Controlled, Multi-Center, Open Label Trial of Lenalidomide/Dexamethasone with or without Elotuzumab in Relapsed or Refractory Multiple Myeloma	Total: 240/635 E-Ld: 119/318 Ld: 121/317	Total: 120/635 E-Ld: 65/318 Ld: 55/317	Total: 5/635 E-Ld: 1/318 Ld: 4/317
CA204009 Phase 2, Randomized, Controlled, Multi-Center, Open-Label Study of Bortezomib/Dexamethasone (Bd) with or without Elotuzumab in Subjects with Relapsed/Refractory Multiple Myeloma	Total: 56/150 E-Bd: 27/75 Bd: 29/75	Total: 28/150 E-Bd: 15/75 Bd: 13/75	Total: 1/150 E-Bd: 0/75 Bd: 1/75

E-Ld: Elotuzumab combined with lenalidomide and dexamethasone; Ld: lenalidomide and dexamethasone; E-Bd: Elotuzumab combined with bortezomib and dexamethasone; Bd: bortezomib and dexamethasone

Table 27. Special Age Populations Treated in Elotuzumab Non-controlled Clinical Studies (Pooled total number: 147/336)

Clinical studies in special populations	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
Non-controlled studies (Pooled, CA204005, CA204007, HuLuc63-1701, HuLuc63-1702, HuLuc63-1703, CA204010, CA204011, and CA204112)	90/336	54/336	3/336
CA204005 Phase 1, Open Label, Dose Escalation Study of Elotuzumab in Combination with Lenalidomide/Low-dose Dexamethasone in Patients with Relapsed or Refractory Multiple Myeloma in Japan	2/6	1/6	0/6
CA204007 Phase 1b, Multi-Center, Open-Label 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	4/26	5/26	1/26
HuLuc63-1701 Phase 1, Multi-Center, Open-Label, Dose Escalation Study of Elotuzumab (Humanized anti-CS1 Monoclonal IgG1 antibody) in Subjects with Advanced Multiple Myeloma	6/34	10/34	1/34
HuLuc63-1702 Phase 1, Multi-Center, Open-label, Dose-escalation Study of Elotuzumab (Humanized anti-CS1 Monoclonal IgG1Antibody) and Bortezomib in Subjects With Multiple Myeloma Following One to Three Prior Therapies	7/28	2/28	0/28

HuLuc63-1703 Phase 1b/2, Multi-Center, Open-label, Dose-escalation Study of Elotuzumab (Humanized Anti-CS1 Monoclonal IgG1 Antibody) in Combination with Lenalidomide and Dexamethasone in Subjects with Relapsed Multiple Myeloma	29/101	9/101	0/101
CA204010 Phase 2A Single Arm Safety Study of Elotuzumab in Combination with Thalidomide and Dexamethasone in Subjects with Relapsed and/or Refractory Multiple Myeloma	12/40	6/40	0/40
CA204011 A Phase 2 Biomarker Study of elotuzumab (Humanized Anti-CS1 Monoclonal Antibody) Monotherapy to Assess the Association between NK cell Status and Efficacy in High Risk Smoldering Myeloma	7/31	1/31	0/31
CA204112 A Phase 2 Single Arm Study of Safety of Elotuzumab Administered over Approximately 60 Minutes in Combination with Lenalidomide and Dexamethasone for Newly Diagnosed or Relapsed/Refractory Multiple Myeloma Patients	23/70	20/70	1/70

Supportive studies

The results from pivotal studies CA204004 and CA204009 were supported by phase 2 study HuLuc63-1703 (E-Ld) and phase 1 study HuLuc63-1702 (E-Bd), described under ''section 2.5.1. Dose response studies''. A summary of the efficacy results in comparison with the pivotal trials is provided in Table 33 and Table 34.

Table 28. Overall Efficacy Summary E-Ld Studies

	CA204004		HuLuc63-1703 - Phase 2
	Treatment Groups[a]		Elotuzumab Dose Groups + Ld[a]
Endpoint[b, c]	Elotuzumab 10 mg/kg +Ld	Ld	Total (10- and 20-mg/kg Doses Combined)
Number of Randomized Subjects	N=321	N=325	N=73
PFS			
Number of Events (%)	179 (55.8)	205 (63.1)	36 (49.32)
Hazard Ratio (E-Ld/Ld) 95% CI 97.61% CI	0.70 (0.57, 0.85) (0.55, 0.88)		Not applicable
... P-value (Significance α Level = 0.0239)	0.0004		
1-year PFS rate (95% CI)	0.68 (0.63, 0.73)	0.57 (0.51, 0.62)	0.78* -
2-year PFS rate (95% CI)	0.41 (0.35, 0.47)	0.27 (0.22, 0.33)	0.56* -
3-year PFS rate (95% CI)	Not determined	Not determined	0.38*
Median (95% CI) (Months)	19.4 (16.6, 22.2)	14.9 (12.1, 17.2)	28.6 (16.6, 43.1)
ORR			
Number of Responders (%)	252 (78.5)	213 (65.5)	61 (83.6)
Exact 95% CI	(73.6, 82.9)	(60.1, 70.7)	73.0, 91.2
Common Odds Ratio	1.94		Not applicable
95% CI	(1.36, 2.77)		
99.5% CI	(1.17, 3.23)		
P-value (Significance α Level = 0.005)	0.0002		

Difference in ORR 95% CI	12.6% (6.1, 19.2)		
TTR[d]			
Number of responders (%)	252 (78.5)	213 (65.5)	61 (83.6)
Median and range (months)	1.9 (<0.1 - 19.6)	1.9 (0.8 - 13.0)	1.0 (0.7 - 19.2)
DOR[d]			
Number of responders (%)	252 (78.5)	213 (65.5)	61 (83.6)
Median (95% CI)	20.7 (17.5, 26.8)	16.6 (14.8, 19.4)	29.2 (18.2, NE)
OS			Not applicable
Number (%) of Events	94 (29.3)	116 (35.7)	
Hazard Ratio (E-Ld/Ld) (95% CI)	0.71 (0.54, 0.93)		
1-year OS rate (95% CI)	0.91 (0.87, 0.93)	0.83 (0.78, 0.87)	
2-year OS rate (95% CI)	0.74 (0.69, 0.79)	0.68 (0.63, 0.73)	
Median (2-sided 95% CI) (Months)	NE (36.2, NE)	34.6 (29.0, NE)	

a Treatment with E-Ld or Ld was administered in 28-day cycles: elotuzumab administered as an IV infusion weekly in C1 & C2 on Days 1, 8, 15, and 22; and in C3 and beyond Q2W on Days 1 and 15; lenalidomide 25 mg po daily on Days 1-21; dexamethasone 40 mg po once weekly on weeks without elotuzumab, and as a split dose of 8 mg IV+28 mg po on weeks with elotuzumab (for Study HuLuc63-1703, this dexamethasone dosing regimen started with Protocol Amendment E).

b Endpoint assessments are per IRC (primary definition, using censoring rules) for CA204004 and per Investigator for HuLuc63-1703.

c Response assessments were based on IMWG criteria for HuLuc63-1703.

d ORR, TTR and DOR determined \ for subjects with best response of PR or better (sCR, CR, VGPR, and PR) for both CA204004 and HuLuc63-1703.

Table 29. Overall Efficacy Summary E-Bd Studies

	CA204009		HuLuc63-1702 - Phase 1
	Treatment Groups[a]		Elotuzumab Dose Groups + Bd
Endpoint[b]	Elotuzumab 10 mg/kg +Bd	Bd	Total (2.5 to 20-mg/kg Doses Combined)
Number of Randomized Subjects	N=77	N=75	N=27
PFS			
Number of Events (%)	52 (67.5)	59 (78.7)	14 (51.85)
Hazard Ratio (E-Bd/Bd) 70% CI 95% CI	0.72 (0.59, 0.88) (0.49, 1.06)		Not applicable
... P-value (Significance α Level = 0.3)	0.0923		Not applicable
1-year PFS rate (95% CI)	0.39 (0.28 , 0.50)	0.33 (0.22 , 0.44)	Not determined
Median (2-sided 95% CI) (Months)	9.7 (7.4, 12.2)	6.9 (5.1, 10.2)	9.46 (5.78-27.17)
ORR[c]			
Number of Responders (%)	50 (64.9)	47 (62.7)	13 (48.1)
95% CI (%)	53.2, 75.5	50.7, 73.6	28.7, 68.1
Difference in ORR(%)	2.3		Not determined
Exact 95% CI for difference in ORR (%)	(-13.2, 17.8)		-
TTR[c]			
Number of responders (%)	50 (64.9)	47 (62.7)	13 (48.1)
Median and range (months)	1.43 (<0.1 - 11.2)	1.51 (<0.0 - 6.7)	2.1 (1.1 - 6.5)
DOR[c]			
Number of responders (%)	50 (64.9)	47 (62.7)	13 (48.1)
Median (95% CI)	10.4 (8.5, 14.8)	9.3 (5.6, 11.7)	6.6 (range:1.4 - 33.9)
OS			
Number (%) of Events	17 (22.1)	23 (30.7)	Not determined
Hazard Ratio (E-Ld/Ld) 95% CI	0.61 (0.32, 1.15)		
1-year OS rate (95% CI)	0.85 (0.75, 0.92)	0.74 (0.62, 0.83)	
Median (2-sided 95% CI) (Months)	NE (23.56, NE)	26.1 (NE, NE)	

a Treatment with E-Bd or Bd was administered as follows: investigational and control groups: bortezomib (Velcade®) 1.3 mg/m2 administered either IV or SC on Days 1, 4, 8, and 11 of C1-8 (21-day cycles); and Days 1, 8, and 15 of C9 and beyond (28-day cycles). Investigational and control groups: dexamethasone 20 mg po administered on Days 1, 2, 4, 5, 8, 9, 11, 12 (control group only), and 15 (investigational group only) of C1 and C2; Days 1, 2, 4, 5, 8, 9, 11, and 12 of C3-8; and Days 1, 2, 8, 9, 15, and 16 of C9 and beyond; on days with elotuzumab (investigational group), it was administered as a split dose of 8 mg IV+8 mg po.

b Endpoint assessments are per Investigator based on IMWG criteria for CA204009 and per Investigator based on EBMT criteria for HuLuc63-1702.

c ORR, DOR, and TTR calculated for subjects with best response of PR or better (sCR, CR, VGPR, and PR) for CA204009 and CR or PR for HuLuc63-1702.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Both pivotal studies were open-label studies which might have influenced efficacy evaluation, although an independent review committee (IRC) was assigned in study CA204004 reviewing all tumour assessment data to determine the best response and date of progression. In contrast, the primary endpoint PFS in study CA204009 was investigator-based, and no IRC was assigned, lowering reliability of the obtained

study results. Reliability of efficacy results could also be considered lower compared to study CA204004 due to the much lower number of included patients in study CA204009 (646 vs. 152).

As the median number of prior treatments was 2 in the population in which the E-Ld combination was investigated and only one prior treatment in the E-Bd study, the E-Ld population is considered more representative of a population who have received one or more prior treatments as in the claimed indication.

The dosage for each combination has been adequately justified and is based on lack of increase of efficacy and even decreased efficacy, at a dose of 20 mg/kg compared to 10 mg/kg possibly due to saturation of elotuzumab binding to SLAMF7.

In study CA204004 demographics and baseline characteristics were well balanced between treatment arms. A limitation of the data on the E-Ld combination is that only 6% of subjects in study CA204004 had received prior lenalidomide therapy and no lenalidomide refractory patients were included. These limitations have been reflected in section 5.1 of the SmPC.

Efficacy data and additional analyses

For the E-Ld regimen, according to the ITT analysis, a statistically significant 4.2 months (18.5 vs. 14.3) improvement in PFS was observed compared with Ld alone (HR=0.68, 95% CI 0.56, 0.83, p=0.0001). The co-primary endpoint ORR showed benefit for the E-Ld combination as well: 78.5% E-Ld vs 65.5% Ld, with a common odds ratio of 1.94. A higher frequency of complete responses was observed within the Ld arm (1.6% E-Ld vs. 5.8% Ld) which is likely due to cross-interference detection of elotuzumab in the SPEP (serum protein electrophoresis) and SIFE (serum immunofixation electrophoresis) assays testing M protein levels.

Efficacy of E-Ld was maintained in patients with up to 3 prior lines of therapy, the population studied in study CA204004. In patients treated with E-Ld, the median PFS was similar in patients with 1, 2 or 3 prior lines of therapy. Median overall survival was similar in patients with 1 or 2 prior lines of therapy and somewhat lower in those with 3 prior lines. Importantly, the benefit in PFS and in OS compared to Ld increased in those with 3 prior lines, justifying it's use in those with more advanced disease. Also in patients with refractory disease, there was clear median PFS benefit of approximately 6 months. In patients with lower risk disease, specifically patients not refractory to prior treatment and those in IMWG standard risk category, PFS benefit was also evident.

Improvements observed in PFS were consistent across subsets regardless of age (< 65 versus ≥ 65), risk status, presence or absence of cytogenetic categories del 17p or t(4;14), ISS stage, number of prior therapies, prior immunomodulatory exposure, prior bortezomib exposure, relapsed or refractory status or renal function (SmPC section 5.1).

For the number of prior lines of therapy, the HR for (PFS ITT definition) for E-Ld vs Ld is similar at 0.71 (0.54, 0.94) and 0.72 (0.51, 1.00) for one or 2 prior lines respectively and is similar to that in the overall population. The PFS benefit (HR) with E-Ld vs Ld for those with 3 prior lines is more favourable at 0.53 (0.33, 0.83) although it should be noted that there were only approximately 50 patients (15%) in each arm with 3 prior therapies compared to approximately 116 in each arm with 2 prior therapies and 150 with one prior therapy.

Noticeably, the HR for OS at 0.92 (0.66,1.29) and also the course of the K-M curves, suggest no benefit for E-Ld compared to Ld for those with only one prior line of therapy.

For those with 2 prior lines, HR for E-LD-vs Ld was 0.73 (0.49, 1.10), and similar to that in the overall population. As for PFS, benefit as reflected in the HR is greater for those with 3 prior lines of therapy (HR 0.56; 95%b CI 0.34, 0.92).

For both study arms, the ORR is fairly similar in those with 1, 2 or 3 prior therapy lines. It was approximately 78% in the E-Ld arm and 66% in the Ld arm for those with 1 or 2 prior lines and for those with 3 prior lines of therapy it was 70 % and 60% in the E-Ld and ld arms respectively

The results of an updated OS analysis (cut-off date of 29 October 2015) with a minimum follow up of 35.4 months showed a similar trend to the initial analysis: A 23% reduction in the risk of death (HR 0.77, 95% CI: 0.61 0.97; p=-0.0257) was observed. Median OS was 43.7 months (95% CI: 40.3, NE) for E-Ld arm versus 39.6 months (95% CI: 33.3, NE) for Ld arm.

The 1-, 2- and 3-year rates of overall survival for Empliciti in combination with lenalidomide and dexamethasone treatment were 91%, 73%, and 60% respectively, compared with 83%, 69%, and 53% respectively, for lenalidomide and dexamethasone treatment (SmPC section 5.1).Compared to the overall population, median PFS and OS in the Prior Systemic Therapy subgroups, each of which represents a separate agent, are not less favourable than in the overall population, except that as only approximately 6% of patients in each arm had received prior lenalidomide no conclusions for that subgroup can be made. According to the inclusion/exclusion criteria, no data on the efficacy of E-Ld in patients with known refractoriness to lenalidomide could be provided.

Unfortunately, except for “no prior IMiD” the PFS and OS data for the subgroups representing patients who had not previously been treated with a particular therapy have not been provided.

With regard to prior SCT, for PFS the HR 0.64 (95% CI: 0.48, 0.85) is somewhat more favourable for those who have not had a prior SCT compared to 0.72 (0.56, 0.93) for those who did have a SCT. For OS there is little difference between prior SCT or not with a HR 0.75 (0.54, 1.05) for those who have not had a prior SCT compared to 0.80 (0.58, 1.09) for those who did have a prior SCT. These hazard ratios are comparable to that in the overall population (HR 0.77 (0.61, 0.97)). For both study arms the ORR is fairly similar in those who did or did not have prior SCT. In a Cox proportional hazards model analysis conducted to evaluate possible confounding factors on PFS, prior stem cell transplantation was indeed one of the statistically significant factors (HR, no prior SCT versus prior SCT= 0.67, P= 0.0032). Rueff et al., (2014) have shown a positive correlation between NK cell count at 1 month after ASCT and PFS, and NK cells are known to play a relevant role in the mechanism of action of Elotuzumab. It is therefore possible that NK cell count at baseline may also have an impact on clinical response to Elotuzumab, and that patients with prior ASCT may have impaired NK cell counts or functionality. The CHMP recommended the applicant to further investigate the association between baseline NK cell counts and PD/clinical endpoints. In particular, a small sub-study in the CA204006 trial in newly diagnosed multiple myeloma patients with elotuzumab in combination withlenalidomide/dexamethasone is currently ongoing and new data will be provided.

These data on subgroups pre-defined according to the number of prior regimens and type of agents with which patients have previously been treated provide reassurance that ORR and PFS benefit of E-Ld compared to Ld in all the subgroups analysed is similar to that seen in the overall population, not forgetting that only approximately 6% of patients in each arm had received prior lenalidomide precluding conclusions on this small subgroup.

For OS, the case is different as, despite a PFS benefit similar to that in the overall population, there is no apparent OS benefit in the large subgroup of those who have had only one prior therapy, representing approximately 50% of the study population. This lack of survival benefit calls into question the ultimate benefit of adding elotuzumab to lenalidomide / dexamethasone in these patients. However, most patients who have had only one prior line of therapy are still at a relatively early stage in their disease and a benefit in OS is less likely to be apparent. Furthermore, the effect of therapies subsequent to E-Ld or Ld will be a major influence on the OS.

The approach of accepting a PFS benefit if there is no detrimental effect on OS was agreed in scientific advice for elotuzumab. As patients with only one prior line of treatment have an expected survival of several years, it can be accepted that for these patients no OS benefit of E-Ld compared to Ld has yet been observed.

Concerning prior systemic therapies, except for IMiDs, it is not possible to evaluate whether receiving a particular prior therapy or not, is associated with a differential response to E-Ld or Ld.

The median PFS advantage with E-Ld in some lower risk subgroups was reduced compared to that observed in the overall population, in particular in: not refractory patients (ITT-PFS advantage over Ld: 2.8 months), patients with no prior treatment with IMiDs (median ITT-PFS advantage: 1.4 months) and IMWG standard risk patients (median ITT-PFS advantage: 3 months).

Apart from the the subgroup of patients who have received no prior IMiD (thalidomide), PFS benefit with E-Ld compared to Ld is evident to varying degrees in the subgroups although it should be taken into consideration that some of these subgroups are very small.

The pattern in the subgroup prior lenalidomide seems similar to that seen with prior thalidomide.i.e. larger PFS benefit than in the overall population, but the prior lenalidomide subgroup was only approximately 6% of the population, meaning that estimations of medians and HR are uncertain.

For the subgroups prior IMiD (thalidomide) vs no prior IMiD there is a large difference between the subgroups in the benefit in median PFS.

In patients who had not had prior IMiD therapy (no lenalidomide or thalidomide) the PFS benefit of E-Ld compared to Ld (approximately 1.4 months) was lower than in the overall population and was higher in patients who had received prior thalidomide therapy (approximately 6 months). However, the thalidomide-exposed population is likely to be very heterogeneous and characteristics of the patients who did or did not have prior thalidomide e.g. number of prior therapy lines, prior SCT, risk category, refractory status, number of prior thalidomide regimens, whether prior thalidomide was received in a SCT regimen, possibly refractory to thalidomide are not known. It is not clear if the difference in PFS is related to prior thalidomide therapy yes/no or to some other factor or a combination of factors.The extent of exposure to thalidomide in these different settings is also likely to be variable and it cannot be excluded that the higher efficacy observed in the IMiD exposed population might have been driven by patients with long-term exposure or who have become refractory to thalidomide. Additional subgroup analyses according to the extent of actual exposure to thalidomide are not expected to provide valuable information. Information has been included in SmPC Section 5.1 on the PFS and HR in the subgroups of those who had prior IMiD (Thal) and no prior IMiD, refractory and not refractory patients, and those with high risk and standard risk MM.

During the assessment the CHMP raised a major objection on the indication regarding the E-Bd combination. In study CA204009 the evidence of a clinically relevant benefit is considered insufficient. In addition, the trial population was limited in number and two thirds of the patients had had only one prior therapy. The indication has now been revised by the applicant and restricted to elotuzumab in combination with lenalidomide and dexamethasone for the treatment of multiple myeloma in adult patients who have received one prior therapy.

2.5.4. Conclusions on the clinical efficacy

The pivotal study CA204004 demonstrated a statistically significant benefit for elotuzumab in combination with lenalidomide and dexamethasone in multiple myeloma patients who have received at least one prior therapy in terms of the primary endpoint PFS. Progression free survvival improvement was supported by ORR benefit. Updated OS data confirmed the trend to OS benefit and the benefit in PFS and

in OS compared to Ld increased in those with 3 prior lines, justifying the use of elotuzumab in patients with more advanced disease. In patients with lower risk disease, specifically patients not refractory to prior treatment and those in IMWG standard risk category, PFS benefit was also evident.

2.6. Clinical safety

The clinical studies supporting safety of elotuzumab are reported and described in details in Table 35.

Table 30. Summary of Clinical Studies Supporting Safety for Elotuzumab

Study Number	Population	Study Design	Number of Elotuzumab Treated Subjects	Status at Time of Database Lock (Primary Endpoint)	Number of Subjects Still on Treatment at Time of Database Lock
IMiD Regimens					
E-Ld Studies					
CA204004[a] (ELOQUENT-2)	Previously treated, relapsed/refractory MM	Phase 3, randomized, open-label, E-Ld vs. Ld	10 mg/kg, N=318	Completed	113
HuLuc63-1703[b]	Previously treated, relapsed/refractory MM	Phase 1b/2, open-label, dose-escalation	5 mg/kg, N=3 10 mg/kg, N=39 20 mg/kg, N=59	Completed	17
CA204005[b]	Previously treated, relapsed/refractory MM (Japanese subjects)	Phase 1, open-label, dose-escalation, Japan	10 mg/kg, N=3 20 mg/kg, N=3	Completed	3
CA204007[b]	Newly diagnosed or relapsed/refractory MM with or without SRI or ESRD	Phase 1b, PK in normal, renal impairment, ESRD	10 mg/kg, N=26	Completed	11 total: 2 NRF 5 SRI 4 ESRD
PI Regimen					
E-Bd Studies					
CA204009[a]	Previously treated, relapsed/refractory MM	Phase 2, single-arm, open-label, E-Bd vs. Bd	10 mg/kg, N=75	Completed	21 total: 14 E-Bd 7 Bd
HuLuc63-1702	Previously treated, relapsed/refractory MM	Phase 1, open-label, dose-escalation	2.5 mg/kg, N=3 5 mg/kg, N=3 10 mg/kg, N=3 20 mg/kg, N=19	Completed	0
Other Supportive Studies					
E-Td Study					
CA204010	Previously treated, relapsed/refractory MM	Phase 2a, single-arm	10 mg/kg, N=40	Completed	13
Elotuzumab Monotherapy					
HuLuc63-1701	Previously treated, relapsed/refractory MM	Phase 1, open-label, dose-escalation	0.5 mg/kg, N=3 1 mg/kg, N=4 2.5 mg/kg, N=6 5 mg/kg, N=4 10 mg/kg, N=3 20 mg/kg, N=14	Completed	0
CA204011	High-risk Smoldering MM	Phase 2, biomarker	10 mg/kg, N=16 20 mg/kg, N=15	Completed	18 total 7 (20 mg/kg) 11 (10 mg/kg)

Ongoing E-Ld Studies					
CA204006	Previously untreated, newly diagnosed, transplant ineligible MM	Phase 3, randomized, open-label, E-Ld vs. Ld	10 mg/kg, N= 371[c]	Ongoing	Ongoing
CA204112	Newly diagnosed or relapsed/refractory MM	Phase 2, single-arm, Elotuzumab administered over approx 60 min with Ld	10 mg/kg, N=69[d]	Ongoing	Ongoing

[a] In Studies CA204004 and CA204009, subjects remaining in the study are on long-term treatment for safety follow-up, OS follow-up ongoing.

[b] Subjects remaining in study are on long-term treatment for safety follow-up.

[c] The number of treated subjects is an estimated number based on 1:1 randomization scheme with a data cut-off of 14-Nov-2014.

[d] The number of treated subjects based on the data cut-off of 15-May-2015.

Bd = bortezomib and dexamethasone, E-Bd = elotuzumab and bortezomib and low-dose dexamethasone, E-Ld = elotuzumab and lenalidomide and low dose dexamethasone, ESRD = end-stage renal disease, E-Td = elotuzumab and thalidomide and low-dose dexamethasone, Ld = lenalidomide and dexamethasone, MM = multiple myeloma, NRF = normal renal function, PI = proteasome inhibitor, PK = pharmacokinetic, SRI = sever renal disease CA = studies sponsored by Bristol-Myers Squibb; HuLuc63 = studies sponsored by AbbVie

Patient exposure

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. Data on the overall elotuzumab exposure are reported in Table 36.

Table 31. Patient exposure

	Patients enrolled	**Patients exposed**	**Patients exposed to the proposed dose range**	**Patients with long term* safety data**
Placebo-controlled	-	-	-	-
Open-Label Active-controlled				
CA204004 (cut-off: 4-Nov-2014)	761	318	318	155 (E-Ld: 101; Ld: 54)
Pool E-Ld	451	451	386 (318 in CA204004; 39 in HuLuc-1703; 3 in CA204005; 26 in CA204007)	140
CA204009 (cut-off: 12-Sep-2014)	185	75	75	-
CA204006 (cut-off: 14-Nov-2014)	-	742	371	-
CA204112 (cut-off: 15-May-2015)	-	69	69	-
Open-Label non-controlled studies				
HuLuc63-1703 (cut-off date: 16-Jan-2014)	102 (Phase 1b: 29; Phase 2: 73)	101 (Phase 1b: 28; Phase 2: 73)	39 (Phase 1b: 3; Phase 2: 36)	-**
HuLuc63-1702	28	28	3	-
CA204005 (cut-off date: 14-Feb-2014)	7	6	3	-**
CA204007(cut-off date: 30-Jun-2014)	35	26	26	-**
CA204010 (19-Feb-2014)	51	40	40	-
HuLuc63-1701	35	34	3	-
CA204011 (8-Sep-2014)	41	31	16	-
Post marketing	-	-	-	-
Compassionate use	-	-	-	-

* In general this refers to 6 months and 12 months continuous exposure data, or intermittent exposure. For study CA204004, "long-term safety data" was referred to the available data on AEs occurred following 24 months of dosing with Elotuzumab in combination with Ld. Available data on long-term safety data for study CA204004 and Pooled E-Ld were presented. It is not specified how many subjects from the E-Ld studies other than CA204004 had a >24-month follow-up to be included in the long-term data of Pooled E-Ld

** It was not specified how many subjects of those still on treatment had a >24-month follow-up period

The relative dose intensity summary for both pivotal studies are presented below in Tables 37 and 38.

Table 32. Relative Dose Intensity by Drug Summary - All Treated Subjects with 10mg/kg Elotuzumab (CA204004 and Pooled E-Ld Population)

	CA204004 E-Ld N=318			Pooled E-Ld[a] N= 386		
	Elotuzumab	Lenalidomide	Dexamethasone	Elotuzumab	Lenalidomide	Dexamethasone
Relative dose intensity						
≥ 90%	264 (83.0)	163 (51.3)	146 (45.9)	315 (81.6)	190 (49.2)	166 (43.0)
80% to < 90%	35 (11.0)	41 (12.9)	61 (19.2)	47 (12.2)	50 (13.0)	74 (19.2)
70% to < 80%	12 (3.8)	27 (8.5)	25 (7.9)	14 (3.6)	33 (8.5)	34 (8.8)
60% to <70%	2 (0.6)	30 (9.4)	26 (8.2)	3 (0.8)	45 (11.7)	32 (8.3)
<60%	5 (1.6)	56 (17.6)	60 (18.9)	7 (1.8)	66 (17.1)	80 (20.7)

[a] Pooled E-Ld: CA204004 (E-Ld), CA204005, CA204007, and HuLuc63-1703

Table 33. Relative Dose Intensity Summary - All Subjects Treated (CA204009)

Adverse events

CA204004 -E-Ld combination

An overview of the summary of Safety Results in study CA204004 is presented in Table 39.

Table 34. Summary of Safety Results - All Treated Subjects (Study CA204004)

	Number (%) of subjects					
	E-Ld (N= 318)			Ld (N= 317)		
Deaths	94 (29.6)			116 (36.6)		
Deaths within 60 days of last dose	31 (9.7)			39 (12.3)		
	Worst Grade			Worst Grade		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
All SAEs	208 (65.4)	153 (48.1)	31 (9.7)	179 (56.5)	116 (36.6)	39 (12.3)
All AEs leading to DC	83 (26.1)	51 (16.0)	17 (5.3)	85 (26.8)	50 (15.8)	20 (6.3)
All AEs	316 (99.4)	247 (77.7)	31 (9.7)	314 (99.1)	208 (65.6)	39 (12.3)
Infusion reactions	33 (10.4)	4 (1.3)	0	NA	NA	NA
Second primary malignancy	22 (6.9)	NA	NA	13 (4.1)	NA	NA

Table 35. Adverse Event with at Least 5 Percent Frequency Summary by CTC Grade Combined - All Treated Subjects (CA204004 and Pooled E-Ld Population)

System Organ Class (%) Preferred Term (%)	CA204004 E-Ld N = 318 Any Grade	CA204004 E-Ld N = 318 Grade 3-4	CA204004 E-Ld N = 318 Grade 5	CA204004 Ld N = 317 Any Grade	CA204004 Ld N = 317 Grade 3-4	CA204004 Ld N = 317 Grade 5	Pooled E-Ld N = 451 Any Grade	Pooled E-Ld N = 451 Grade 3-4	Pooled E-Ld N = 451 Grade 5
TOTAL SUBJECTS WITH AN EVENT	316 (99.4)	247 (77.7)	31 (9.7)	314 (99.1)	208 (65.6)	39 (12.3)	449 (99.6)	352 (78.0)	35 (7.8)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	263 (82.7)	63 (19.8)	10 (3.1)	237 (74.8)	49 (15.5)	12 (3.8)	384 (85.1)	82 (18.2)	11 (2.4)
FATIGUE	149 (46.9)	27 (8.5)	0	123 (38.8)	26 (8.2)	0	226 (50.1)	38 (8.4)	0
PYREXIA	119 (37.4)	8 (2.5)	0	78 (24.6)	9 (2.8)	0	173 (38.4)	10 (2.2)	0
OEDEMA PERIPHERAL	82 (25.8)	4 (1.3)	0	70 (22.1)	1 (0.3)	0	118 (26.2)	5 (1.1)	0
ASTHENIA	70 (22.0)	15 (4.7)	0	53 (16.7)	12 (3.8)	0	99 (22.0)	17 (3.8)	0
CHILLS	24 (7.5)	0	0	13 (4.1)	0	0	41 (9.1)	0	0
CHEST PAIN	26 (8.2)	2 (0.6)	0	11 (3.5)	1 (0.3)	0	32 (7.1)	4 (0.9)	0
LOCAL SWELLING	10 (3.1)	0	0	5 (1.6)	0	0	26 (5.8)	0	0
MALAISE	18 (5.7)	4 (1.3)	0	11 (3.5)	0	0	26 (5.8)	4 (0.9)	0
INFLUENZA LIKE ILLNESS	19 (6.0)	1 (0.3)	0	15 (4.7)	1 (0.3)	0	25 (5.5)	2 (0.4)	0
GASTROINTESTINAL DISORDERS	254 (79.9)	31 (9.7)	0	213 (67.2)	27 (8.5)	1 (0.3)	372 (82.5)	49 (10.9)	1 (0.2)
DIARRHOEA	149 (46.9)	16 (5.0)	0	114 (36.0)	13 (4.1)	0	227 (50.3)	29 (6.4)	0
CONSTIPATION	113 (35.5)	4 (1.3)	0	86 (27.1)	1 (0.3)	0	178 (39.5)	5 (1.1)	0
NAUSEA	76 (23.9)	3 (0.9)	0	68 (21.5)	2 (0.6)	0	133 (29.5)	4 (0.9)	0
VOMITING	46 (14.5)	1 (0.3)	0	28 (8.8)	3 (0.9)	0	72 (16.0)	2 (0.4)	0
ABDOMINAL PAIN	39 (12.3)	1 (0.3)	0	27 (8.5)	0	0	57 (12.6)	1 (0.2)	0
DYSPEPSIA	32 (10.1)	0	0	19 (6.0)	0	0	47 (10.4)	0	0
STOMATITIS	27 (8.5)	0	0	14 (4.4)	0	0	41 (9.1)	0	0
ABDOMINAL PAIN UPPER	22 (6.9)	1 (0.3)	0	17 (5.4)	0	0	31 (6.9)	1 (0.2)	0
INFECTIONS AND INFESTATIONS	259 (81.4)	89 (28.0)	8 (2.5)	236 (74.4)	77 (24.3)	7 (2.2)	368 (81.6)	121 (26.8)	10 (2.2)
UPPER RESPIRATORY TRACT INFECTION	72 (22.6)	2 (0.6)	0	55 (17.4)	4 (1.3)	0	120 (26.6)	6 (1.3)	0
NASOPHARYNGITIS	78 (24.5)	0	0	61 (19.2)	0	0	105 (23.3)	0	0
BRONCHITIS	55 (17.3)	5 (1.6)	0	51 (16.1)	7 (2.2)	0	79 (17.5)	8 (1.8)	0
PNEUMONIA	48 (15.1)	33 (10.4)	2 (0.6)	37 (11.7)	23 (7.3)	0	66 (14.6)	43 (9.5)	3 (0.7)
URINARY TRACT INFECTION	27 (8.5)	4 (1.3)	0	31 (9.8)	7 (2.2)	0	45 (10.0)	5 (1.1)	0
RHINITIS	23 (7.2)	0	0	12 (3.8)	0	0	38 (8.4)	0	0
RESPIRATORY TRACT INFECTION	34 (10.7)	8 (2.5)	0	30 (9.5)	4 (1.3)	0	36 (8.0)	8 (1.8)	0
INFLUENZA	19 (6.0)	2 (0.6)	1 (0.3)	21 (6.6)	4 (1.3)	0	32 (7.1)	4 (0.9)	1 (0.2)
SINUSITIS	20 (6.3)	1 (0.3)	0	14 (4.4)	1 (0.3)	0	32 (7.1)	2 (0.4)	0
LOWER RESPIRATORY TRACT INFECTION	27 (8.5)	3 (0.9)	1 (0.3)	17 (5.4)	4 (1.3)	0	28 (6.2)	4 (0.9)	1 (0.2)
HERPES ZOSTER	19 (6.0)	5 (1.6)	0	9 (2.8)	2 (0.6)	0	24 (5.3)	6 (1.3)	0
CELLULITIS	12 (3.8)	5 (1.6)	0	7 (2.2)	1 (0.3)	0	23 (5.1)	6 (1.3)	1 (0.2)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	219 (68.9)	42 (13.2)	0	215 (67.8)	36 (11.4)	0	325 (72.1)	61 (13.5)	0
MUSCLE SPASMS	95 (29.9)	1 (0.3)	0	84 (26.5)	3 (0.9)	0	157 (34.8)	3 (0.7)	0
BACK PAIN	90 (28.3)	16 (5.0)	0	89 (28.1)	14 (4.4)	0	137 (30.4)	22 (4.9)	0
ARTHRALGIA	53 (16.7)	4 (1.3)	0	39 (12.3)	2 (0.6)	0	85 (18.8)	7 (1.6)	0
PAIN IN EXTREMITY	52 (16.4)	3 (0.9)	0	32 (10.1)	1 (0.3)	0	82 (18.2)	3 (0.7)	0
MUSCULOSKELETAL PAIN	41 (12.9)	5 (1.6)	0	28 (8.8)	2 (0.6)	0	55 (12.2)	8 (1.8)	0
BONE PAIN	33 (10.4)	1 (0.3)	0	40 (12.6)	3 (0.9)	0	48 (10.6)	3 (0.7)	0
MUSCULAR WEAKNESS	37 (11.6)	6 (1.9)	0	25 (7.9)	4 (1.3)	0	43 (9.5)	7 (1.6)	0
MUSCULOSKELETAL CHEST PAIN	32 (10.1)	1 (0.3)	0	26 (8.2)	0	0	42 (9.3)	2 (0.4)	0
MYALGIA	22 (6.9)	0	0	23 (7.3)	0	0	34 (7.5)	1 (0.2)	0
NERVOUS SYSTEM DISORDERS	203 (63.8)	35 (11.0)	0	172 (54.3)	29 (9.1)	2 (0.6)	303 (67.2)	50 (11.1)	0
HEADACHE	49 (15.4)	1 (0.3)	0	24 (7.6)	1 (0.3)	0	78 (17.3)	2 (0.4)	0
NEUROPATHY PERIPHERAL	45 (14.2)	5 (1.6)	0	26 (8.2)	5 (1.6)	0	73 (16.2)	6 (1.3)	0
DIZZINESS	45 (14.2)	2 (0.6)	0	37 (11.7)	0	0	70 (15.5)	2 (0.4)	0
DYSGEUSIA	32 (10.1)	0	0	20 (6.3)	0	0	55 (12.2)	0	0
PARAESTHESIA	32 (10.1)	1 (0.3)	0	29 (9.1)	1 (0.3)	0	45 (10.0)	1 (0.2)	0
PERIPHERAL SENSORY NEUROPATHY	29 (9.1)	4 (1.3)	0	35 (11.0)	2 (0.6)	0	39 (8.6)	4 (0.9)	0
TREMOR	29 (9.1)	2 (0.6)	0	29 (9.1)	1 (0.3)	0	39 (8.6)	2 (0.4)	0
HYPOAESTHESIA	22 (6.9)	1 (0.3)	0	11 (3.5)	0	0	31 (6.9)	1 (0.2)	0

BLOOD AND LYMPHATIC SYSTEM DISORDERS	201 (63.2)	137 (43.1)	1 (0.3)	193 (60.9)	143 (45.1)	0	293 (65.0)	204 (45.2)	1 (0.2)			
ANAEMIA	124 (39.0)	48 (15.1)	0	117 (36.9)	52 (16.4)	0	178 (39.5)	64 (14.2)	0			
NEUTROPENIA	107 (33.6)	79 (24.8)	0	135 (42.6)	105 (33.1)	0	148 (32.8)	110 (24.4)	0			
THROMBOCYTOPENIA	86 (27.0)	37 (11.6)	0	72 (22.7)	36 (11.4)	0	124 (27.5)	60 (13.3)	0			
LYMPHOPENIA	42 (13.2)	28 (8.8)	0	22 (6.9)	10 (3.2)	0	76 (16.9)	53 (11.8)	0			
LEUKOPENIA	24 (7.5)	13 (4.1)	0	25 (7.9)	12 (3.8)	0	51 (11.3)	24 (5.3)	0			
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	193 (60.7)	30 (9.4)	2 (0.6)	164 (51.7)	24 (7.6)	1 (0.3)	284 (63.0)	47 (10.4)	2 (0.4)			
COUGH	100 (31.4)	1 (0.3)	0	57 (18.0)	0	0	138 (30.6)	1 (0.2)	0			
DYSPNOEA	69 (21.7)	6 (1.9)	0	59 (18.6)	11 (3.5)	0	101 (22.4)	12 (2.7)	0			
OROPHARYNGEAL PAIN	32 (10.1)	0	0	14 (4.4)	0	0	44 (9.8)	0	0			
DYSPHONIA	24 (7.5)	0	0	30 (9.5)	1 (0.3)	0	37 (8.2)	0	0			
DYSPNOEA EXERTIONAL	18 (5.7)	0	0	13 (4.1)	0	0	36 (8.0)	0	0			
EPISTAXIS	19 (6.0)	2 (0.6)	0	19 (6.0)	0	0	32 (7.1)	3 (0.7)	0			
PRODUCTIVE COUGH	19 (6.0)	0	0	4 (1.3)	0	0	28 (6.2)	0	0			
NASAL CONGESTION	10 (3.1)	0	0	6 (1.9)	0	0	24 (5.3)	0	0			
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	185 (58.2)	9 (2.8)	0	144 (45.4)	8 (2.5)	0	269 (59.6)	13 (2.9)	0			
RASH	58 (18.2)	1 (0.3)	0	58 (18.3)	5 (1.6)	0	91 (20.2)	3 (0.7)	0			
HYPERHIDROSIS	37 (11.6)	0	0	22 (6.9)	0	0	54 (12.0)	0	0			
PRURITUS	32 (10.1)	0	0	28 (8.8)	0	0	43 (9.5)	0	0			
NIGHT SWEATS	22 (6.9)	0	0	9 (2.8)	0	0	41 (9.1)	0	0			
ERYTHEMA	22 (6.9)	0	0	17 (5.4)	0	0	34 (7.5)	0	0			
METABOLISM AND NUTRITION DISORDERS	177 (55.7)	63 (19.8)	0	153 (48.3)	51 (16.1)	0	257 (57.0)	92 (20.4)	1 (0.2)			
DECREASED APPETITE	66 (20.8)	5 (1.6)	0	40 (12.6)	4 (1.3)	0	92 (20.4)	6 (1.3)	0			
HYPERGLYCAEMIA	55 (17.3)	23 (7.2)	0	43 (13.6)	14 (4.4)	0	87 (19.3)	36 (8.0)	0			
HYPOKALAEMIA	53 (16.7)	15 (4.7)	0	47 (14.8)	15 (4.7)	0	80 (17.7)	22 (4.9)	0			
HYPOCALCAEMIA	43 (13.5)	10 (3.1)	0	31 (9.8)	4 (1.3)	0	56 (12.4)	13 (2.9)	0			
HYPONATRAEMIA	19 (6.0)	4 (1.3)	0	12 (3.8)	5 (1.6)	0	28 (6.2)	6 (1.3)	0			
HYPOALBUMINAEMIA	15 (4.7)	0	0	11 (3.5)	1 (0.3)	0	25 (5.5)	0	0			
INVESTIGATIONS	153 (48.1)	35 (11.0)	0	122 (38.5)	31 (9.8)	1 (0.3)	216 (47.9)	55 (12.2)	0			
WEIGHT DECREASED	44 (13.8)	4 (1.3)	0	19 (6.0)	0	0	59 (13.1)	4 (0.9)	0			
BLOOD CREATININE INCREASED	30 (9.4)	1 (0.3)	0	22 (6.9)	0	1 (0.3)	45 (10.0)	5 (1.1)	0			
ALANINE AMINOTRANSFERASE INCREASED	24 (7.5)	1 (0.3)	0	32 (10.1)	8 (2.5)	0	39 (8.6)	5 (1.1)	0			
ASPARTATE AMINOTRANSFERASE INCREASED	20 (6.3)	0	0	28 (8.8)	7 (2.2)	0	31 (6.9)	2 (0.4)	0			
PSYCHIATRIC DISORDERS	135 (42.5)	17 (5.3)	1 (0.3)	121 (38.2)	14 (4.4)	0	201 (44.6)	23 (5.1)	1 (0.2)			
INSOMNIA	73 (23.0)	6 (1.9)	0	82 (25.9)	8 (2.5)	0	114 (25.3)	8 (1.8)	0			
ANXIETY	23 (7.2)	0	0	21 (6.6)	1 (0.3)	0	36 (8.0)	0	0			
DEPRESSION	16 (5.0)	0	0	14 (4.4)	4 (1.3)	0	26 (5.8)	1 (0.2)	0			
CONFUSIONAL STATE	20 (6.3)	5 (1.6)	0	11 (3.5)	2 (0.6)	0	25 (5.5)	7 (1.6)	0			
MOOD ALTERED	22 (6.9)	0	0	8 (2.5)	0	0	23 (5.1)	0	0			
VASCULAR DISORDERS	116 (36.5)	29 (9.1)	1 (0.3)	85 (26.8)	23 (7.3)	0	159 (35.3)	40 (8.9)	1 (0.2)			
HYPOTENSION	30 (9.4)	3 (0.9)	0	12 (3.8)	3 (0.9)	0	39 (8.6)	3 (0.7)	0			
HYPERTENSION	29 (9.1)	4 (1.3)	0	19 (6.0)	6 (1.9)	0	37 (8.2)	6 (1.3)	0			
DEEP VEIN THROMBOSIS	23 (7.2)	18 (5.7)	0	12 (3.8)	7 (2.2)	0	33 (7.3)	23 (5.1)	0			
FLUSHING	16 (5.0)	0	0	6 (1.9)	0	0	25 (5.5)	0	0			
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	109 (34.3)	10 (3.1)	0	85 (26.8)	14 (4.4)	2 (0.6)	156 (34.6)	12 (2.7)	0			
CONTUSION	36 (11.3)	1 (0.3)	0	26 (8.2)	0	0	48 (10.6)	1 (0.2)	0			
FALL	13 (4.1)	0	0	11 (3.5)	0	0	25 (5.5)	0	0			
EYE DISORDERS	98 (30.8)	25 (7.9)	0	71 (22.4)	10 (3.2)	0	143 (31.7)	30 (6.7)	0			
CATARACT	38 (11.9)	20 (6.3)	0	20 (6.3)	9 (2.8)	0	50 (11.1)	24 (5.3)	0			
VISION BLURRED	27 (8.5)	1 (0.3)	0	16 (5.0)	1 (0.3)	0	48 (10.6)	1 (0.2)	0			

Table 36. Adverse Event with at Least 5 Percent Frequency Summary by CTC Grade Combined - All Treated Subjects (CA204009)

System Organ Class (%) Preferred Term (%)	E-Bd N = 75			Bd N = 75		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
PERIPHERAL SENSORY NEUROPATHY	7 (9.3)	0	0	8 (10.7)	0	0
TREMOR	3 (4.0)	0	0	5 (6.7)	0	0
DYSGEUSIA	1 (1.3)	0	0	4 (5.3)	0	0
SOMNOLENCE	0	0	0	7 (9.3)	1 (1.3)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	51 (68.0)	8 (10.7)	0	40 (53.3)	5 (6.7)	0
PAIN IN EXTREMITY	17 (22.7)	1 (1.3)	0	12 (16.0)	1 (1.3)	0
BACK PAIN	14 (18.7)	2 (2.7)	0	14 (18.7)	1 (1.3)	0
BONE PAIN	14 (18.7)	2 (2.7)	0	7 (9.3)	1 (1.3)	0
MUSCLE SPASMS	7 (9.3)	0	0	5 (6.7)	0	0
MUSCULAR WEAKNESS	6 (8.0)	1 (1.3)	0	2 (2.7)	0	0
ARTHRALGIA	5 (6.7)	0	0	11 (14.7)	1 (1.3)	0
MUSCULOSKELETAL CHEST PAIN	5 (6.7)	0	0	8 (10.7)	1 (1.3)	0
MUSCULOSKELETAL PAIN	4 (5.3)	0	0	3 (4.0)	0	0
INFECTIONS AND INFESTATIONS	49 (65.3)	13 (17.3)	1 (1.3)	40 (53.3)	10 (13.3)	1 (1.3)
UPPER RESPIRATORY TRACT INFECTION	10 (13.3)	0	0	4 (5.3)	0	0
CONJUNCTIVITIS	7 (9.3)	0	0	5 (6.7)	0	0
NASOPHARYNGITIS	6 (8.0)	0	0	8 (10.7)	0	0
PNEUMONIA	6 (8.0)	5 (6.7)	0	9 (12.0)	5 (6.7)	0
BRONCHITIS	5 (6.7)	0	0	7 (9.3)	0	0
HERPES ZOSTER	5 (6.7)	1 (1.3)	0	3 (4.0)	0	0
CELLULITIS	4 (5.3)	1 (1.3)	0	0	0	0
INFLUENZA	3 (4.0)	0	0	7 (9.3)	0	0
URINARY TRACT INFECTION	3 (4.0)	1 (1.3)	0	5 (6.7)	0	0
RESPIRATORY TRACT INFECTION	1 (1.3)	0	0	4 (5.3)	1 (1.3)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	45 (60.0)	6 (8.0)	0	41 (54.7)	5 (6.7)	0
COUGH	29 (38.7)	1 (1.3)	0	17 (22.7)	0	0
DYSPNOEA	13 (17.3)	1 (1.3)	0	8 (10.7)	0	0
EPISTAXIS	8 (10.7)	1 (1.3)	0	2 (2.7)	0	0
DYSPHONIA	5 (6.7)	0	0	0	0	0
OROPHARYNGEAL PAIN	4 (5.3)	0	0	7 (9.3)	0	0
PRODUCTIVE COUGH	3 (4.0)	0	0	6 (8.0)	0	0
INVESTIGATIONS	38 (50.7)	12 (16.0)	0	25 (33.3)	6 (8.0)	0
PLATELET COUNT DECREASED	11 (14.7)	5 (6.7)	0	12 (16.0)	6 (8.0)	0
WEIGHT DECREASED	7 (9.3)	0	0	3 (4.0)	0	0
BLOOD CREATININE INCREASED	4 (5.3)	1 (1.3)	0	3 (4.0)	0	0
WEIGHT INCREASED	4 (5.3)	0	0	4 (5.3)	0	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	34 (45.3)	11 (14.7)	0	35 (46.7)	23 (30.7)	0
ANAEMIA	28 (37.3)	5 (6.7)	0	21 (28.0)	5 (6.7)	0
THROMBOCYTOPENIA	12 (16.0)	7 (9.3)	0	20 (26.7)	13 (17.3)	0
NEUTROPENIA	5 (6.7)	2 (2.7)	0	10 (13.3)	5 (6.7)	0
METABOLISM AND NUTRITION DISORDERS	31 (41.3)	15 (20.0)	0	30 (40.0)	8 (10.7)	0
DECREASED APPETITE	12 (16.0)	0	0	11 (14.7)	0	0
HYPERGLYCAEMIA	10 (13.3)	9 (12.0)	0	6 (8.0)	4 (5.3)	0
HYPOCALCAEMIA	9 (12.0)	0	0	2 (2.7)	0	0
HYPOKALAEMIA	9 (12.0)	4 (5.3)	0	5 (6.7)	0	0
HYPONATRAEMIA	5 (6.7)	2 (2.7)	0	2 (2.7)	1 (1.3)	0
PSYCHIATRIC DISORDERS	29 (38.7)	0	0	21 (28.0)	1 (1.3)	0
INSOMNIA	22 (29.3)	0	0	14 (18.7)	1 (1.3)	0
ANXIETY	7 (9.3)	0	0	2 (2.7)	0	0
CONFUSIONAL STATE	4 (5.3)	0	0	3 (4.0)	0	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	24 (32.0)	2 (2.7)	0	23 (30.7)	0	0
RASH	8 (10.7)	0	0	5 (6.7)	0	0
HYPERHIDROSIS	4 (5.3)	0	0	2 (2.7)	0	0
PRURITUS	3 (4.0)	0	0	6 (8.0)	0	0
DRY SKIN	2 (2.7)	0	0	5 (6.7)	0	0
VASCULAR DISORDERS	22 (29.3)	4 (5.3)	0	20 (26.7)	3 (4.0)	0
HYPERTENSION	11 (14.7)	2 (2.7)	0	4 (5.3)	0	0
HYPOTENSION	4 (5.3)	1 (1.3)	0	6 (8.0)	1 (1.3)	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	16 (21.3)	1 (1.3)	0	11 (14.7)	3 (4.0)	1 (1.3)
RIB FRACTURE	5 (6.7)	0	0	2 (2.7)	0	0
EYE DISORDERS	15 (20.0)	1 (1.3)	0	17 (22.7)	1 (1.3)	0
VISION BLURRED	4 (5.3)	0	0	6 (8.0)	0	0
CATARACT	1 (1.3)	0	0	4 (5.3)	1 (1.3)	0
CARDIAC DISORDERS	11 (14.7)	2 (2.7)	0	11 (14.7)	4 (5.3)	1 (1.3)
TACHYCARDIA	3 (4.0)	0	0	5 (6.7)	1 (1.3)	0

Adverse Reactions

Table 37. Adverse reactions in patients with multiple myeloma treated with Empliciti (SmPC Section 4.8)

System Organ Class	Adverse reactions	Frequency overall	Grade 3/4 frequency
Infections and infestations	Herpes zostera	Very Common	Common
	Nasopharyngitis	Very Common	None reported
	Pneumoniab	Very Common	Very Common
	Upper respiratory tract infection	Very Common	Common
Blood and lymphatic system disorders	Lymphopeniac	Very common	Very common
Immune system disorders	Anaphylactic reaction	Uncommon	Uncommon
	Hypersensitivity	Common	Uncommon
Psychiatric disorders	Mood altered	Common	None reported
Nervous system disorders	Headache	Very Common	Uncommon
	Hypoaesthesia	Common	Uncommon
Vascular disorders	Deep vein thrombosis	Common	Common
Respiratory, thoracic and mediastinal disorders	Coughd	Very Common	Uncommon
	Oropharyngeal pain	Common	None reported
Gastrointestinal disorders	Diarrhoea	Very Common	Common
Skin and subcutaneous tissue disorders	Night sweats	Common	None reported
General disorders and administration site conditions	Chest pain	Common	Common
	Fatigue	Very Common	Common
	Pyrexia	Very Common	Common
Investigations	Weight decreased	Very common	Uncommon
Injury, poisoning and procedural complications	Infusion related reaction	Common	Common

[a] The term herpes zoster is a grouping of the following terms: herpes zoster, oral herpes, and herpes virus infection.
b The term pneumonia is a grouping of the following terms: pneumonia, atypical pneumonia, bronchopneumonia, lobar pneumonia, bacterial pneumonia, fungal pneumonia, pneumonia influenza, and pneumococcal pneumonia.
c The term lymphopenia includes the following terms: lymphopenia and lymphocyte count decreased.
d The term cough includes the following terms: cough, productive cough, and upper airway cough syndrome.

Exposure-adjusted rates for adverse reactions (all Grades and Grade 3/4) in Study CA204004, is shown in Table 43.

Table 38. Exposure-adjusted rates for adverse reactions for Empliciti-treated patients versus lenalidomide and dexamethasone-treated patients [includes multiple occurrences of all treated patients] (Study CA204004) (SmPC Section 4.8)

	Empliciti + Lenalidomide and Dexamethasone N = 318				**Lenalidomide and Dexamethasone N = 317**			
	All grades		**Grade 3/4**		**All grades**		**Grade 3/4**	
Adverse reaction	**Event count**	**Rate (incidence rate/100 patient years)**	**Event count**	**Rate (incidence rate/100 patient years)**	**Event count**	**Rate (incidence rate/100 patient years)**	**Event count**	**Rate (incidence rate/100 patient years)**
Diarrhoea	303	59.2	19	3.7	206	49.3	13	3.1
Pyrexia	220	43.0	8	1.6	116	27.7	10	2.4
Fatigue	205	40.0	33	6.4	145	34.7	26	6.2
Cough[a]	170	33.2	1	0.2	85	20.3	-	-
Nasopharyngitis	151	29.5	-	-	116	27.7	-	-
Upper respiratory tract infection	129	25.2	2	0.4	95	22.7	4	1.0
Lymphopenia[b]	90	17.6	65	12.7	57	13.6	31	7.4
Headache	88	17.2	1	0.2	40	9.6	1	0.2
Pneumonia[c]	80	15.6	54	10.5	54	12.9	34	8.1
Herpes zoster[d]	51	10.0	5	1.0	24	5.7	3	0.7
Oropharyngeal pain	45	8.8	-	-	17	4.1	-	-
Weight decreased	44	8.6	4	0.8	20	4.8	-	-
Night sweats	31	6.1	-	-	12	2.9	-	-
Chest pain	29	5.7	2	0.4	12	2.9	1	0.2
Deep vein thrombosis	26	5.1	18	3.5	12	2.9	7	1.7
Hypoaethesia	25	4.9	1	0.2	12	2.9	-	-
Mood altered	23	4.5	-	-	8	1.9	-	-
Hypersensitivity	10	2.0	-	-	4	1.0	1	0.2

[a] The term cough includes the following terms: cough, productive cough, and upper airway cough syndrome.
[b] The term lymphopenia includes the following terms: lymphopenia and lymphocyte count decreased.
[c] The term pneumonia is a grouping of the following terms: pneumonia, atypical pneumonia, bronchopneumonia, lobar pneumonia, bacterial pneumonia, fungal pneumonia, pneumonia influenza, and pneumococcal pneumonia.
[d] The term herpes zoster is a grouping of the following terms: herpes zoster, oral herpes, and herpes virus infection.

Adverse events of special interest

Infusion reactions

All ongoing elotuzumab studies were amended in 2010, after the Grade 3 infusion AEs were observed in the Phase 1 program with studies HuLuc63-1701, HuLuc63-1702, and Phase 1b portion of Huluc63-1703, to ensure that all subjects received premedication with IV corticosteroids, oral or IV diphenhydramine, and oral acetaminophen prior to each elotuzumab infusion. Hence, all subjects treated in the Phase 2 portion of HuLuc63-1703 received this amended premedication regimen.

In CA204004 study, infusion reactions were reported in approximately 10% of premedicated patients treated with Empliciti combined with lenalidomide and dexamethasone (N = 318) (see section 4.4). The rate of mild to moderate infusion reactions was > 50% in patients who were not premedicated. All reports of infusion reaction were ≤ Grade 3. Grade 3 infusion reactions occurred in 1% of patients. The most common symptoms of an infusion reaction included fever, chills, and hypertension. Five percent (5%) of patients required interruption of the administration of Empliciti for a median of 25 minutes due to infusion reaction, and 1% of patients discontinued due to infusion reactions. Of the patients who experienced an infusion reaction, 70% (23/33) had the reaction during the first dose (SmPC section 4.8).

In the submitted elotuzumab trials, an infusion rate escalation plan was implemented (in combination with guidelines for the safety management of IRs and premedication administration) to shorten the infusion time of elotuzumab from 2 1/2 hours (0.5 mL/minute every 30 minutes to a maximum of 2 mL/min) to approximately 1 hour (up to 5 mL/min).

The results of the faster infusion rate are presented for 2 randomized trials (HuLuc63-1703 and CA204009 and 1 ongoing trial (CA204112). In study CA204004, only very few infusions were given at a faster rate (of 12,581 infusions there were 40 infusions at >2ml/min, of which 11 ⩾ 5 mL/min) and they did not lead to new or additional IR events.

- HuLuc63-1703 (E-Ld): 31 patients in the phase 2 portion had an infusion rate escalated up to 5 mL/min. Only 1 patient experienced a grade 1 event of nausea at the highest infusion rate, which was considered an IR. The faster 5 mL/min infusion rate appeared as safe as the 2 mL/min infusion rate with no increase in IRs at 5 mL/min.
- CA204009 (E-Bd): No infusion reactions were reported among the 36% of patients in the E-Bd treatment group who had infusions administered at a faster rate of 5 mL/min.
- CA204112 (E-Ld): Preliminary data of this ongoing study (using a similar escalation strategy as proposed in the elotuzumab SmPC) showed one grade 2 IR of the 69 patients treated for at least 2 months or more. This grade 2 IR led to study drug interruption.

Second primary malignancies

In CA204004 study, invasive SPMs have been observed in 6.9% of patients treated with Empliciti combined with lenalidomide and dexamethasone (N = 318) and 4.1% of patients treated with lenalidomide and dexamethasone (N = 317). The rate of haematologic malignancies was the same between the two treatment arms (1.6%). Solid tumours were reported in 2.5% and 1.9% of Empliciti combined with lenalidomide and dexamethasone and lenalidomide and dexamethasone treated patients, respectively. Non-melanoma skin cancer was reported in 3.1% and 1.6% of patients treated with Empliciti combined with lenalidomide and dexamethasone and lenalidomide and dexamethasone, respectively (SmPC section 4.8).

Table 39. Second Primary Malignancies – All Treated Patients Study CA204004

	CA204004	
	E-Ld N = 318	Ld N = 317
NUMBER OF SUBJECTS WITH SECOND PRIMARY MALIGNANCY	22 (6.9)	13 (4.1)
DIAGNOSIS (PREFERRED TERM)		
SQUAMOUS CELL CARCINOMA OF SKIN	7 (2.2)	2 (0.6)
MYELODYSPLASTIC SYNDROME	3 (0.9)	5 (1.6)
BASAL CELL CARCINOMA	3 (0.9)	3 (0.9)
SQUAMOUS CELL CARCINOMA	1 (0.3)	1 (0.3)
LUNG NEOPLASM MALIGNANT	3 (0.9)	1 (0.3)
MALIGNANT NEOPLASM OF UNKNOWN PRIMARY SITE	1 (0.3)	1 (0.3)
PROSTATE CANCER	0	1 (0.3)
BLADDER CANCER	1 (0.3)	0
BREAST CANCER	1 (0.3)	0
CHRONIC LYMPHOCYTIC LEUKAEMIA	1 (0.3)	0
ERYTHROLEUKAEMIA	1 (0.3)	0
GASTROINTESTINAL NEOPLASM	1 (0.3)	0
LUNG ADENOCARCINOMA	1 (0.3)	0
PLEURAL MESOTHELIOMA MALIGNANT	1 (0.3)	0
ADENOCARCINOMA OF COLON	0	1 (0.3)
ENDOMETRIAL CANCER	0	1 (0.3)
REFRACTORY ANAEMIA WITH AN EXCESS OF BLASTS	0	1 (0.3)
TONSIL CANCER	0	1 (0.3)

In study CA204009 2.7% (n=2: breast cancer and basal cell carcinoma) had a SPM in the E-Bd arm, vs. 1.3% (n=1: squamous cell carcinoma of the skin) in the Bd arm.

Infections

In study CA204004, infections were reported in 81.4% of patients in the Empliciti combined with lenalidomide and dexamethasone arm (N=318) and 74.4% in lenalidomide and dexamethasone arm (N = 317). Grade 3-4 infections were noted in 28% and 24.3% of Empliciti combined with lenalidomide and dexamethasone and lenalidomide and dexamethasone treated patients, respectively. Fatal infections were infrequent and were reported in 2.5% of Empliciti combined with lenalidomide and dexamethasone and 2.2% of lenalidomide and dexamethasone treated patients. The incidence of pneumonia was higher in the Empliciti combined with lenalidomide and dexamethasone arm compared to lenalidomide and dexamethasone arm reported at 15.1% vs. 11.7% with a fatal outcome at 0.6% vs. 0%, respectively (SmPC section 4.8).

The median absolute lymphocyte count at time of infection was 0.7 (Grade 1) in the E-Ld arm, and $1.0x10^9$/L in the Ld arm. Median time to first infection of any grade was similar in both treatment groups (2.3 months with E-Ld and 2.7 with Ld). The median duration was similar as well (13 and 12.5 days, respectively).

For patients with prior stem cell transplant, a higher frequency of infections was observed in the E-Ld arm (87.4%) compared to the Ld arm (75.8%). There was no difference in Grade 3-4 lymphopenia between E-Ld patients with or without prior SCT (78% and 75%, respectively). For patients without prior stem cell transplantation, the frequency of infections was similar between treatment groups (74.8% E-Ld and 72.7% Ld).

The total number of deaths due to infection within 60 days of last study drug, regardless of relationship to study therapy, was 10 patients in the E-Ld group and 7 in the Ld group. This included the categories infection, study drug toxicity, disease and other.

Of the 10 patients in the E-Ld arm, 7 were included in the category of infection, 2 within study drug toxicity, and 1 in the category of disease: The types of infection AEs reported were: purulent meningitis, sepsis, right pneumopathy, septic shock, Pseudomonas aerouginosa sepsis, disease progression and complications due to infection, influenza virus B infection, lower respiratory tract infection related to IV dexamethasone (1 subject for each event), and pneumonia (2 subjects).

Of the 7 patients in the Ld arm, 2 subjects were included in the category of infection, 4 within study drug toxicity, and 1 in the category of other (bronchopneumonia, fatal): The types of infection AEs reported were: sepsis (3 subjects), fatal bronchopneumonia, Pneumocystitis pneumonia, acute peritonitis, and possible septic shock (1 subject for each event).

A summary of Infections and Infestations reported in study CA204004 is presented in Table 45.

Table 40. Summary of Infections and Infestations – All Treated Patients (CA204004)

	Number (%) of subjects					
	E-Ld N= 318			Ld N= 317		
	Worst Grade			Worst Grade		
Infections and Infestations	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
SAEs of Inf	99 (31.1)	76 (23.9)	8 (2.5)	80 (25.2)	63 (19.9)	7 (2.2)
Any AE of Inf leading to DC	11 (3.5)	6 (1.9)	4 (1.3)	13 (4.1)	5 (1.6)	7 (2.2)
Any AE Inf	259 (81.4)	89 (28.0)	8 (2.5)	236 (74.4)	77 (24.3)	7 (2.2)
Inf AEs ≥5%						
Nasopharyngitis	78 (24.5)	0	0	61 (19.2)	0	0
Upper respiratory tract infection	72 (22.6)	2 (0.6)	0	55 (17.4)	4 (1.3)	0
Bronchitis	55 (17.3)	5 (1.6)	0	51 (16.1)	7 (2.2)	0
Pneumonia	48 (15.1)	33 (10.4)	2 (0.6)	37 (11.7)	23 (7.3)	0
Respiratory tract infection	34 (10.7)	8 (2.5)	0	30 (9.5)	4 (1.3)	0
Lower respiratory tract infection	27 (8.5)	3 (0.9)	1 (0.3)	17 (5.4)	4 (1.3)	0
Urinary tract infection	27 (8.5)	4 (1.3)	0	31 (9.8)	7 (2.2)	0
Rhinitis	23 (7.2)	0	0	12 (3.8)	0	0
Sinusitis	20 (6.3)	1 (0.3)	0	14 (4.4)	1 (0.3)	0
Herpes zoster	19 (6.0)	5 (1.6)	0	9 (2.8)	2 (0.6)	0
Influenza	19 (6.0)	2 (0.6)	1 (0.3)	21 (6.6)	4 (1.3)	0
Oral herpes	17 (5.3)	0	0	13 (4.1)	0	0
Pharyngitis	17 (5.3)	1 (0.3)	0	12 (3.8)	1 (0.3)	0

Source: refer to Table S.6.2, Table S.6.7, Table S.6.8, and Table S.6.9 in CA204004 CSI
Abbreviations: AE, adverse event; DC, discontinuation; Inf, infection; NA, not applicable; SAE, serious advers event

In study CA204009, AEs of infection of any grade occurred more frequently in the E-Ld arm (65.3% E-Bd vs 53.3% Bd). SAEs of any grade in 21.3% vs 16.0%. The most common Grade 3-4 infection was pneumonia, occurring in a similar percentage of both arms (6.7%).

Deep vein thrombosis

In Study CA204004, deep vein thromboses were reported in 7.2% of patients treated with Empliciti combined with lenalidomide and dexamethasone (N = 318) and 3.8% of patients treated with lenalidomide and dexamethasone (N = 317). Among, patients treated with aspirin, deep vein thromboses were reported in 4.1% of patients treated with Empliciti combined with lenalidomide and dexamethasone

(E Ld) and 1.4% of patients treated with lenalidomide and dexamethasone (Ld). The rates of deep vein thromboses observed between treatment arms were similar for patients given prophylaxis with low molecular weight heparin (2.2% in both treatment arms), and for patients given vitamin K antagonists the rates were 0% for patients treated with E Ld and 6.7% for patients treated with Ld (SmPC section 4.8).

Serious adverse event / deaths / other significant events

Serious adverse event

Table 41. Serious Adverse Event with at Least 1% Frequency Summary by CTC Grade Combined - All Treated Subjects

System Organ Class (%) Preferred Term (%)	E-Ld N = 318			Ld N = 317		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	208 (65.4)	153 (48.1)	31 (9.7)	179 (56.5)	116 (36.6)	39 (12.3)
INFECTIONS AND INFESTATIONS	99 (31.1)	76 (23.9)	8 (2.5)	80 (25.2)	63 (19.9)	7 (2.2)
PNEUMONIA	35 (11.0)	29 (9.1)	2 (0.6)	27 (8.5)	20 (6.3)	0
RESPIRATORY TRACT INFECTION	10 (3.1)	7 (2.2)	0	4 (1.3)	3 (0.9)	0
BRONCHITIS	7 (2.2)	4 (1.3)	0	7 (2.2)	4 (1.3)	0
BRONCHOPNEUMONIA	6 (1.9)	6 (1.9)	0	3 (0.9)	2 (0.6)	1 (0.3)
CELLULITIS	5 (1.6)	4 (1.3)	0	0	0	0
SEPSIS	5 (1.6)	3 (0.9)	2 (0.6)	6 (1.9)	2 (0.6)	3 (0.9)
LOWER RESPIRATORY TRACT INFECTION	4 (1.3)	2 (0.6)	1 (0.3)	3 (0.9)	2 (0.6)	0
URINARY TRACT INFECTION	3 (0.9)	2 (0.6)	0	5 (1.6)	5 (1.6)	0
INFLUENZA	2 (0.6)	1 (0.3)	1 (0.3)	5 (1.6)	4 (1.3)	0
SEPTIC SHOCK	2 (0.6)	1 (0.3)	1 (0.3)	5 (1.6)	4 (1.3)	1 (0.3)
GASTROENTERITIS VIRAL	1 (0.3)	0	0	4 (1.3)	3 (0.9)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	46 (14.5)	16 (5.0)	10 (3.1)	29 (9.1)	7 (2.2)	12 (3.8)
PYREXIA	22 (6.9)	4 (1.3)	0	15 (4.7)	5 (1.6)	0
DISEASE PROGRESSION	13 (4.1)	5 (1.6)	7 (2.2)	10 (3.2)	2 (0.6)	7 (2.2)
GENERAL PHYSICAL HEALTH DETERIORATION	6 (1.9)	2 (0.6)	2 (0.6)	4 (1.3)	0	4 (1.3)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	32 (10.1)	22 (6.9)	7 (2.2)	28 (8.8)	15 (4.7)	10 (3.2)
SQUAMOUS CELL CARCINOMA OF SKIN	6 (1.9)	4 (1.3)	0	2 (0.6)	1 (0.3)	0
MALIGNANT NEOPLASM PROGRESSION	5 (1.6)	2 (0.6)	3 (0.9)	4 (1.3)	0	4 (1.3)
PLASMA CELL MYELOMA	5 (1.6)	3 (0.9)	2 (0.6)	5 (1.6)	1 (0.3)	4 (1.3)
BASAL CELL CARCINOMA	4 (1.3)	4 (1.3)	0	3 (0.9)	3 (0.9)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	32 (10.1)	23 (7.2)	2 (0.6)	19 (6.0)	12 (3.8)	1 (0.3)
PULMONARY EMBOLISM	10 (3.1)	9 (2.8)	1 (0.3)	8 (2.5)	7 (2.2)	1 (0.3)
DYSPNOEA	4 (1.3)	2 (0.6)	0	4 (1.3)	3 (0.9)	0
LUNG DISORDER	4 (1.3)	2 (0.6)	1 (0.3)	1 (0.3)	0	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	20 (6.3)	16 (5.0)	1 (0.3)	15 (4.7)	13 (4.1)	0
ANAEMIA	9 (2.8)	7 (2.2)	0	6 (1.9)	6 (1.9)	0
FEBRILE NEUTROPENIA	5 (1.6)	3 (0.9)	1 (0.3)	4 (1.3)	3 (0.9)	0
THROMBOCYTOPENIA	5 (1.6)	5 (1.6)	0	2 (0.6)	2 (0.6)	0
GASTROINTESTINAL DISORDERS	18 (5.7)	10 (3.1)	0	22 (6.9)	15 (4.7)	1 (0.3)
DIARRHOEA	5 (1.6)	3 (0.9)	0	8 (2.5)	7 (2.2)	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	17 (5.3)	7 (2.2)	0	19 (6.0)	14 (4.4)	2 (0.6)
RENAL AND URINARY DISORDERS	17 (5.3)	9 (2.8)	1 (0.3)	16 (5.0)	9 (2.8)	1 (0.3)
RENAL FAILURE ACUTE	8 (2.5)	4 (1.3)	0	6 (1.9)	4 (1.3)	1 (0.3)
RENAL FAILURE	4 (1.3)	3 (0.9)	0	5 (1.6)	5 (1.6)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	16 (5.0)	15 (4.7)	0	14 (4.4)	12 (3.8)	0
BACK PAIN	5 (1.6)	5 (1.6)	0	5 (1.6)	5 (1.6)	0
CARDIAC DISORDERS	15 (4.7)	11 (3.5)	1 (0.3)	22 (6.9)	15 (4.7)	3 (0.9)
ATRIAL FIBRILLATION	6 (1.9)	4 (1.3)	0	8 (2.5)	6 (1.9)	0
NERVOUS SYSTEM DISORDERS	14 (4.4)	12 (3.8)	0	16 (5.0)	11 (3.5)	2 (0.6)
METABOLISM AND NUTRITION DISORDERS	13 (4.1)	11 (3.5)	0	10 (3.2)	6 (1.9)	0
VASCULAR DISORDERS	11 (3.5)	9 (2.8)	1 (0.3)	10 (3.2)	8 (2.5)	0
DEEP VEIN THROMBOSIS	5 (1.6)	4 (1.3)	0	4 (1.3)	4 (1.3)	0
HEPATOBILIARY DISORDERS	9 (2.8)	8 (2.5)	0	1 (0.3)	0	0
EYE DISORDERS	7 (2.2)	6 (1.9)	0	4 (1.3)	4 (1.3)	0
CATARACT	5 (1.6)	4 (1.3)	0	4 (1.3)	4 (1.3)	0
PSYCHIATRIC DISORDERS	7 (2.2)	3 (0.9)	1 (0.3)	1 (0.3)	1 (0.3)	0
CONFUSIONAL STATE	4 (1.3)	2 (0.6)	0	1 (0.3)	1 (0.3)	0
INVESTIGATIONS	5 (1.6)	4 (1.3)	0	4 (1.3)	3 (0.9)	1 (0.3)

Table 42. Summary of (S)AEs – All Treated Patients (CA204009)

	E-Bd N=75	Bd N=75
AE any grade (%, IR/100 P-Y) - Overall	100%	96%
Diarrhea	42.7% (74.7)	33.3% (75.1)
Peripheral neuropathy	34.7% (49.8)	33.3% (54.4)
Constipation	38.7% (45.6)	29.3% (63.8)
Cough	38.7% (49.8)	22.7% (35.7)
Pyrexia	33.3% (48.4)	26.7% (45)
Asthenia	26.7% (34.6)	28% (43.2)
Peripheral edema	29.3% (33.2)	24% (39.4)
Fatigue	26.7% (33.2)	25.3% (35.7)
Insomnia	29.3% (34.6)	18.7% (30)
Nausea	25.3% (40.1)	21.3% (31.9)
Paresthesia	26.7% (34.6)	18.7% (31.9)
Grade 3-4 AEs – Overall	68%	60%
Non-hematologic		
Hyperglycemia	12%	5.3%
Diarrhea	8%	4%
Pneumonia	6.7%	6.7%
Hypokalemia	5.3%	0%
Peripheral Neuropathy	8%	9.3%
Hematologic		
Thrombocytopenia	9.3%	17.3%
Anemia	6.7%	6.7%
Neutropenia	2.7%	6.7%
SAE any grade - Overall	46.7%	41.3%
Pneumonia	8.0%	5.3%
Cellulitis	2.7%	0%
Sepsis	1.3%	2.7%
Cardiorespiratory arrest	0%	2.7%
Hyperglycemia	2.7%	0%
Small intestine obstruction	0%	2.7%
Vomiting	1.3%	2.7%
Diarrhea	5.3%	1.3%
Abdominal pain	2.7%	1.3%
Nausea	2.7%	1.3%
Peripheral edema	2.7%	0%
Pyrexia	1.3%	4%
Malignant neoplasm progression	2.7%	1.3%
Syncope	4.0%	1.3%
Renal failure	2.7%	1.3%
Renal failure acute	0%	2.7%

Deaths

In study CA204004, with deaths reported as of database cut- off (29-Oct-2014) 29.6% (n=94) of patients in the E-Ld group and 36.6% (n=116) in the Ld group died. The majority of all deaths were due to disease progression in both treatment groups (18.9%, n=60 in the E-Ld group and 24.6%, n=78 in the Ld group). Other primary causes of death in the E-Ld and Ld groups included infection (5.0% vs. 2.8%), cardiovascular disease (0.9% vs. 2.2%), and study drug toxicity (1.6% and 1.9%, respectively).

In the pooled E-Ld population the required time period for reporting of death varied between the studies. In total 22% (n=99) of the patients had died, of which 13.3% due to disease progression. The other primary causes were similar to study CA204004, but with different frequencies: infection (3.5%), cardiovascular disease (0.7%) and study drug toxicity (1.1%).

Table 43. Summary of Deaths - All Treated Subjects (CA204004)

	E-Ld N = 318	Ld N = 317	Total N = 635
NUMBER OF SUBJECTS WHO DIED	94 (29.6)	116 (36.6)	210 (33.1)
PRIMARY CAUSE OF DEATH:			
DISEASE	60 (18.9)	78 (24.6)	138 (21.7)
STUDY DRUG TOXICITY	5 (1.6)	6 (1.9)	11 (1.7)
INFECTION	16 (5.0)	9 (2.8)	25 (3.9)
OTHER MALIGNANCY/NEOPLASM	2 (0.6)	3 (0.9)	5 (0.8)
CARDIOVASCULAR DISEASE	3 (0.9)	7 (2.2)	10 (1.6)
FATAL BLEEDING	1 (0.3)	4 (1.3)	5 (0.8)
OTHER	2 (0.6)	6 (1.9)	8 (1.3)
UNKNOWN	5 (1.6)	3 (0.9)	8 (1.3)

In study CA204009, as of the database lock date 12-Sep-2014, 40 subjects (26.7%) had died: 22.7% (n=17) of patients had died in the E-Bd arm, and 30.7% (n=23) in the Bd arm (Table 44).

Table 44. Summary of Deaths - All Treated Subjects (CA204009)

	E-Bd N=75	**Bd N=75**	**Total N=150**
All Deaths	17 (22.7)	23 (30.7)	40 (26.7)
Primary cause of death:			
Disease	14 (18.7)	16 (21.3)	30 (20.0)
Study drug toxicity	1 (1.3)	0	1 (0.7)
Infection	1 (1.3)	3 (4.0)	4 (2.7)
Cardiovascular disease	0	2 (2.7)	2 (1.3)
Fatal bleeding	0	1 (1.3)	1 (0.7)
Other	1 (1.3)	1 (1.3)	2 (1.3)
Deaths within 60 days of last dose	2 (2.7)	6 (8.0)	8 (5.3)
Primary cause of death:			
Disease	2 (2.7)	2 (2.7)	4 (2.7)
Infection	0	1 (1.3)	1 (0.7)
Cardiovascular disease	0	2 (2.7)	2 (1.3)
Fatal bleeding	0	1 (1.3)	1 (0.7)

Laboratory findings

Haematology

CA204004 -E-Ld combination

Table 45. Grade 3-4 Hematologic Laboratory Tests – All Treated Patients (CA204004 and Pooled E-Ld population)

	CA204004		Pooled E-Ld Population
Hematologic laboratory tests	E-Ld N=318 n (%)	Ld N=317 n (%)	N=451 n (%)
Anemia	60 (18.9)	67 (21.2)	82 (18.2)
Thrombocytopenia	61 (19.2)	64 (20.3)	79 (17.6)
Leukopenia	103 (32.4)	81 (25.6)	144 (32)
Lymphopenia	244 (76.7)	154 (48.7)	348 (78.2)
Neutropenia	107 (33.6)	138 (43.7)	144 (32.4)

CA204009 -E-Bd combination

Table 46. Grade 3-4 Hematologic Laboratory Tests – All Treated Patients (CA204009)

Hematologic laboratory tests	E-Bd N=75 n (%)	Bd N=75 n (%)
Anemia	2 (2.7)	10 (13.5)
Thromobcytopenia	18 (24.7)	25 (33.8)
Leukopenia	5 (6.8)	10 (13.5)
Lymphopenia	44 (60.3)	36 (48.6)
Neutropenia	4 (5.5)	11 (14.9)

Chemistry

CA204004 -E-Ld combination

In study CA204004, Grade 3-4 chemistry laboratory test results occurring more frequently in the E-Ld arm were: hyperkalemia (6.6% vs. 1.6% Ld), hypokalemia (11.6% vs. 9.2%), hypocalcemia (11.3% vs. 5%) and hyperglycaemia (17% vs 10.2%). Hyper-/hyponatremia, and hypercalcemia occurred in similar frequencies in both treatment arms (0.3%, ~10.4% and ~2.5%, respectively). No pooled E-Ld data were provided.

CA204009 -E-Bd combination

In study CA204009, Grade 3-4 chemistry laboratory results occurring more frequently in the E-Bd arm were: hyperkalemia (5.5% E-Bd vs. 1.4% Bd), hypokalemia (8.2% vs. 4.1%) and hyperglycaemia (17.8% vs. 8.1%).

Renal and hepatic function

CA204004 and CA204009

Table 47. Grade 3-4 Renal and Hepatic Laboratory tests (CA204004 and CA204009)

	CA204004		CA204009	
Renal and Hepatic Laboratory Tests n (%)	E-Ld N=318	Ld N=317	E-Bd N=75	Bd N=75
Creatinine	8 (2.5)	9 (2.8)	4 (5.50)	0 (0)
Aspartate aminotransferase	9 (2.8)	8 (2.5)	2 (2.8)	0 (0)
Alanine aminotransferase	16 (5)	13 (4.1)	3 (4.1)	0 (0)
Total bilirubin	8 (2.5)	2 (0.6)	0	0 (0)

Electrocardiograms

The effects of elotuzumab treatment on the QT/QTc interval, as well as AEs potentially related to ECG intervals, was assessed in elotuzumab-treated subjects from Studies CA204004 and CA204011 who consented to participate in the ECG sub-studies. Overall, elotuzumab treatment was not associated with meaningful prolongation of the QTc interval and no safety concerns were evident based on ECG results for subjects treated with elotuzumab across the clinical development program. An assessment of the clinical database did not uncover any AEs (e.g., seizure/convulsion, syncope/presyncope, ventricular arrhythmias) that were considered potentially related to ECG findings.

Safety in special populations

Table 48. CA204004 - AEs and SAEs by Age

	< 65 Years		>= 65 and < 75 Years		>= 75 Years	
Category, Group or SMQ/SOC/HLGT/PT (%) Serious Criteria (%)	E-Ld N = 133	Ld N = 137	E-Ld N = 119	Ld N = 121	E-Ld N = 66	Ld N = 59
TOTAL SUBJECTS WITH AN EVENT	132 (99.2)	136 (99.3)	118 (99.2)	119 (98.3)	66 (100.0)	59 (100.0)
TOTAL SUBJECTS WITH A SERIOUS EVENT	86 (64.7)	66 (48.2)	75 (63.0)	76 (62.8)	47 (71.2)	37 (62.7)
REQUIRES OR PROLONGS HOSPITALIZATION	83 (62.4)	60 (43.8)	68 (57.1)	69 (57.0)	42 (63.6)	34 (57.6)
RESULTS IN DEATH	6 (4.5)	11 (8.0)	18 (15.1)	17 (14.0)	10 (15.2)	13 (22.0)
OTHER MEDICALLY IMPORTANT SERIOUS EVENT	9 (6.8)	13 (9.5)	10 (8.4)	5 (4.1)	9 (13.6)	2 (3.4)
INVOLVES CANCER	2 (1.5)	4 (2.9)	9 (7.6)	6 (5.0)	5 (7.6)	2 (3.4)
IS LIFE THREATENING	2 (1.5)	9 (6.6)	3 (2.5)	8 (6.6)	3 (4.5)	4 (6.8)
PERSIST OR SIGNIF DISABILITY/INCAPACITY	0	0	3 (2.5)	0	1 (1.5)	1 (1.7)
TOTAL SUBJECTS WITH AN EVENT THAT LED TO DISCONTINUATION	30 (22.6)	26 (19.0)	33 (27.7)	31 (25.6)	20 (30.3)	28 (47.5)
INFECTIONS AND INFESTATIONS (SOC)	110 (82.7)	103 (75.2)	92 (77.3)	86 (71.1)	57 (86.4)	47 (79.7)
NERVOUS SYSTEM DISORDERS (SOC)	86 (64.7)	70 (51.1)	72 (60.5)	68 (56.2)	45 (68.2)	34 (57.6)
ANTICHOLINERGIC SYNDROME (SMQ)	83 (62.4)	59 (43.1)	64 (53.8)	59 (48.8)	39 (59.1)	26 (44.1)
PSYCHIATRIC DISORDERS (SOC)	60 (45.1)	56 (40.9)	46 (38.7)	48 (39.7)	29 (43.9)	17 (28.8)
VASCULAR DISORDERS (SOC)	43 (32.3)	38 (27.7)	48 (40.3)	30 (24.8)	25 (37.9)	17 (28.8)
ACCIDENTS AND INJURIES (SMQ)	38 (28.6)	32 (23.4)	38 (31.9)	30 (24.8)	23 (34.8)	17 (28.8)
SUM OF POSTURAL HYPOTENSION, FALLS, BLACKOUT, SYNCOPE, DIZZINESS, ATAXIA AND FRACTURES	30 (22.6)	30 (21.9)	34 (28.6)	25 (20.7)	22 (33.3)	21 (35.6)
CARDIAC DISORDERS (SOC)	16 (12.0)	20 (14.6)	27 (22.7)	19 (15.7)	15 (22.7)	15 (25.4)
CEREBROVASCULAR DISORDERS (SMQ)	4 (3.0)	7 (5.1)	0	5 (4.1)	2 (3.0)	3 (5.1)
QUALITY OF LIFE DECREASED (PT)	0	1 (0.7)	0	0	0	0
AES APPEARING MORE FREQUENTLY IN OLDER PATIENTS (A)	64 (48.1)	66 (48.2)	73 (61.3)	62 (51.2)	47 (71.2)	34 (57.6)
THROMBOCYTOPENIA	35 (26.3)	36 (26.3)	27 (22.7)	20 (16.5)	24 (36.4)	16 (27.1)
OEDEMA PERIPHERAL	18 (13.5)	24 (17.5)	36 (30.3)	27 (22.3)	28 (42.4)	19 (32.2)
ASTHENIA	24 (18.0)	17 (12.4)	27 (22.7)	25 (20.7)	19 (28.8)	11 (18.6)
CONFUSIONAL STATE	3 (2.3)	5 (3.6)	7 (5.9)	4 (3.3)	10 (15.2)	2 (3.4)
HYPONATRAEMIA	4 (3.0)	9 (6.6)	6 (5.0)	1 (0.8)	9 (13.6)	2 (3.4)

Renal impairment

In study CA204004 and CA204009, no patients with severe renal impairment (CrCl<30 mL/min) were included. Phase 1 study CA204007 evaluated the safety of elotuzumab in newly diagnosed and R/R MM subjects with and without renal impairment. Eight patients with a normal renal function (NRF; CrCl ≥90 mL/min), 9 patients with severe renal disease (SRI; CrCl<30 mL/min) not requiring dialysis, and 9 patients with end-stage renal disease (ESRD; requiring hemodialysis) were included and treated with E-Ld.

The percentage of AEs and Grade 3-4 AEs were balanced between the three subgroups (Table 54). However, the frequency of SAEs was higher for SRI and ESRD patients (55.6% and 77.8%, respectively) compared with patients with normal renal function (37.5%). Four patients had AEs leading to discontinuation: n=3 (33.3%) in the SRI group and n=1 (12.5%) in the NRF group. In addition, more infusion reactions were reported for the ESRD arm (22.2% vs 12.5% NRF). The numbers analysed are however small, hampering interpretation of safety results.

Table 49 Summary of TEAEs in renal impairment: All Treated Patients (CA204007)

	NRF N = 8[a]	SRI N = 9[a]	ESRD N = 9[a]
Deaths	0	0	0
Subjects with any SAE, All Grade 3, N (%)	3 (37.5)	5 (55.6)	7 (77.8)
Subjects with an AE			
Any Grade, N (%)	8 (100.0)	9 (100.0)	9 (100.0)
Grade 3 - 4	7 (87.5)	8 (88.9)	7 (77.8)
Subjects with AEs Leading to Study Discontinuation, N (%)[b]	1 (12.5)	3 (33.3)	0
Infusion Reactions (all Grade 2), N (%)	1 (12.5)	0	2 (22.2)
Secondary Malignancies	0	0	0

[a] All Treated include subjects treated with E-Ld

[b] AE and SAE leading to discontinuation are events with an action of discontinuation of any study drug.

Includes AE and SAE with onset on or after the first dosing date and on or prior to the last dosing date +60 days.

Source: refer to Table 8.1-1 in CA204007 CSR

Abbreviations: AE = adverse event; ESRD - end stage renal disease; N = number; NRF = normal renal function; SAE = serious adverse event; SRI = severe renal impairment.

Hepatic impairment

No patients with moderate or severe hepatic impairment have been included in elotuzumab studies. This information is included in SmPC section 4.2.

Safety related to drug-drug interactions and other interactions

No specific safety issues related to possible drug-drug interaction were identified (see also discussion on clinical pharmacology).

Discontinuation due to adverse events

CA204004 -E-Ld combination

In study CA204004, AEs leading to discontinuation (1 or more study drugs) occurred in 26.1 % of subjects in the E-Ld group and 26.8 in the Ld group. The type of events was also similar, with the most frequent occurring event (≥ 2%) of any grade in both treatment groups being disease progression (3.1% and 1.3%). The proportion of subjects with Grade 3-4 was similar in both treatment groups (16.0% in the

E-Ld group and 15.8% in Ld group). Infections represented 3.5% in the E-Ld group and 4.1% in the Ld group of all AEs leading to discontinuation. Overall, there was no difference between treatment groups in the grade or type of infection leading to discontinuation.

A similar pattern was observed in the E-Ld pooled population.

CA204009 -E-Bd combination

In study CA204009, 28% (n=21) of patients discontinued 1 or more study drugs due to AEs in the E-Bd group compared to 34.7% (n=26) in the Bd group. The most common grade 3-4 AEs leading to discontinuation (i.e., in ≥2 patients) in the E-Bd group were thrombocytopenia (2.7%, n=2) and diarrhoea (2.7%, n=2). In the Bd group these were pneumonia (4%, n=3), peripheral neuropathy (4%, n=3), paraesthesia (4%, n=3), and orthostatic hypotension (2.7%, n=2). A similar percentage of patients discontinued 1 or more study drugs to infections of any grade in the E-Bd and Bd groups (5.3%, n=4).

Post marketing experience

Not applicable.

2.6.1. Discussion on clinical safety

The safety data of elotuzumab have been assessed from a total of 554 patients with multiple myeloma treated with elotuzumab in combination with lenaolidomide and dexamethasone (451 patients) or bortezomib and dexamethasone (103 patients) pooled across 6 clinical trials. The majority of adverse reactions were mild to moderate (Grade 1 or 2)(SmPC section 4.8).

Across the 2 randomized, controlled trials CA204004 and CA204009, the median duration of therapy was approximately 5 months longer in the elotuzumab arm compared with the control arms (19 cycles E-Ld vs 14 cycles Ld; and 12 cycles E-Bd vs. 7 cycles Bd). In the E-Ld study, a similar relative dose intensity was observed for lenalidomide and dexamethasone in both treatment arms. In the E-Bd study, slightly less patients received ≥90% of the planned dexamethasone dose in the E-Bd arm (41.3% E-Bd vs 52% Bd), and similarly more dexamethasone dose modifications were observed (82.7% E-Bd vs. 68% Bd). The bortezomib dose intensity was similar between treatment arms, although more bortezomib dose reductions were observed in the E-Bd arm (48.6% vs. 39.2% Bd).

In both pivotal studies, the frequency of discontinuation due to study drug toxicity (all study drugs) was similar between the elotuzumab and control arms, or even lower with elotuzumab (E-Bd setting). In study CA204004 (E-Ld) 2 patients discontinued study therapy with elotuzumab due to an infusion reaction and in study CA204009 (E-Bd) none did. In study CA204004, discontinuation of either one of the three products of the E-Ld therapy was low (overall 2%), similarly divided over the three treatments and were mostly the result of adverse events and are not considered to bias the results.

In the first two cycles treatment was administered weekly and in subsequent cycles the time interval between doses was longer. Adverse events do accumulate over time, as would be expected to occur in a myeloma population, as seen in the Ld and Bd arms of the CA204004 and CA204009 studies, respectively. Overall, there is a steady accumulation of AEs over time in all arms of the studies presented, however, no added cumulative treatment effect can be demonstrated with elotuzumab.

Adverse Events

Almost all patients in the two pivotal trials experienced an AE. As expected, higher frequencies of grade 3-4 AEs (78% E-Ld vs 66% Ld; 68% E-Bd vs 60% Bd) , and SAEs (65% E-Ld vs. 56% Ld; 47% E-Bd vs. 41% Bd) were observed with the addition of elotuzumab to Ld or Bd. In the E-Ld regimen, haematological grade 3-4 AEs were most prominent (primarily lymphopenia and leukopenia), whereas in the E-Bd

regimen non-hematological grade 3-4 AEs occurred with the highest frequency (mostly hyperglycaemia and diarrhoea).

The majority of adverse reactions were mild to moderate (Grade 1 or 2). The most common adverse reactions (occurring in > 10% of patients) with elotuzumab treatment were cough, herpes zoster, nasopharyngitis, pneumonia, upper respiratory tract infection and weight decreased.

With both regimens Grade 3-4 SAEs were observed >10% more frequent in the elotuzumab arm compared with Ld or Bd alone (48.1% E-Ld vs 36.6% Ld; and 37.3% E-Bd vs. 26.7% Bd). The most serious adverse reaction that may occur during elotuzumab treatment is pneumonia (SmPC section 4.8).

For both Study CA204004 and CA204009, the majority of the most prevalent AEs and SAEs resolved. The median durations of events were generally similar between the arms.

In study CA204004, more patients died in the control arm compared to the elotuzumab arm, which is reassuring. However the signal for pulmonary infection observed with the grade 3-4 SAEs is also found in causes of death. In the E-Ld study, more patients died due to infection in the E-Ld arm compared with the Ld arm (2.2%, n=7 E-Ld vs. 0.6%, n=2 Ld). Of these infections, 4 in the E-Ld arm, and none in the Ld arm were related to the pulmonary tract. Overall, in study CA204004, among the deaths identified as “study drug toxicity”-related, infection was the most frequently reported cause; pulmonary embolism was reported as “study drug toxicity”-related cause of death with a similar proportion in the treatment groups. Of note, one case of death due to gastrointestinal tumour in the E-Ld group was classified under the term ‘‘study drug toxicity”.

Infections

Multiple myeloma is associated with immune dysfunction, and elotuzumab may inhibit cellular components of the immune system, which both may increase the risk for infection. Apart from an increase in SAEs of infection (31% vs 25%) and deaths (n=7 vs n=2) due to infection in the E-Ld arm, a higher frequency of infection AEs (81% vs. 74%) and grade 3-4 AEs (28% vs. 24%) were observed. The imbalance in infection rate was most prominent in patients with prior stem cell transplant (87.4% E-Ld compared to 75.8% Ld: 12% difference), independent of the frequency of lymphopenia.

These safety data indicated that infection is an important identified risk of elotuzumab treatment, which might be life-threatening. No measurable factor or characteristic was identified in the elotuzumab-treated population that could predict susceptibility to an infection. Most of the measurable factors were similar between the two study cohorts.

A lower proportion of subjects with neutropenia were observed when elotuzumab was added to both Ld and Bd regimen compared to Ld and Bd groups (E-Ld vs. Ld: 33.6% vs. 43.7%; E-Bd vs. Bd: 4 subjects [5.5%] vs. 11 subjects [14.9%]). The similar rate of infections observed with elotuzumab in the exposure-adjusted analysis may have thus been driven by the unexplained higher rates of neutropenia in the control groups, but this remains unclear.

Patients with prophylactic therapy had a lower frequency of infection than those without prophylactic anti-infective in both treatment arms, although the differences are small. There was also a reduction in the frequency of Grade 3-4 infections in both arms. No difference is seen in the time to first infection, and the duration of infection, across all arms, regardless of the presence of prophylaxis or treatment arm. It is acknowledged that these data could be confounded given that prophylaxis was not mandatory, and subjects at highest risk for infection were given antibacterial and/or antivirals.

Patients should be monitored and infections should be managed with standard treatment (SmPC, section 4.4). Infections have been classified as an important identified risk in the Risk Management Plan.

Infusion Reactions

Nearly all mAbs including elotuzumab share a risk for standard infusion reactions (IRs). With the use of premedication, IRs occurred in approximately 10% of elotuzumab treated patients. They were usually mild to moderate and manageable using recommended guidelines for premedication. A faster infusion rate (up to 5 mL/min in subjects tolerating elotuzumab at 2 mL/min) did not affect the incidence of IRs or introduce new safety concerns. With the use of pre-medication no clinically meaningful immunogenicity to elotuzumab was observed with E-Ld and E-Bd treatment.

Premedication consisting of dexamethasone, H1 blocker, H2 blocker, and paracetamol must be administered prior to Empliciti infusion (SmPC section 4.2). The rate of infusion reactions was much higher in patients who were not premedicated. In case of a Grade ≥ 2 infusion reaction, Empliciti infusion must be interrupted and appropriate medical and supportive measures instituted. Vital signs should be monitored every 30 minutes for 2 hours after the end of the Empliciti infusion. Once the reaction has resolved (≤ Grade 1) Empliciti can be restarted at the initial infusion rate of 0.5 mL per minute. If symptoms do not recur, the infusion rate may be gradually escalated every 30 minutes to a maximum of 5 mL per minute (SmPC section 4.4).

Anti-drug antibodies

No safety concerns seem to arise from immunogenicity data. In CA204004 study the incidence of infusion reactions (IRs) among subjects with anti drug antibodies (ADA) (16% of 45 ADA positive subjects) is higher than in ADA negative subjects (9% of 254 ADA negative subjects but were similar in the CA204009 study (5% of 20 ADA positive subjects vs 6% of 52 ADA negative subjects). A clear temporal or causal relationship to occurrence of ADAs and IRs cannot be established based on the limited data. Infusion reactions have been classified as an important identified risk in the Risk Management Plan.

Second Primary Malignancies

The addition of elotuzumab to lenalidomide did slightly increase the occurrence of SPMs (6.9% E-Ld vs 4.1% Ld), even when corrected for exposure duration. The imbalance was mostly caused by the occurrence of squamous cell carcinoma of the skin, and for other SPMs no clear pattern in type was observed. Slightly more patients in the E-Ld arm were diagnosed with a SPM at study entry or had received prior melphalan treatment compared with the Ld arm, which might explain the imbalance. It is reassuring that the frequency of SPMs is in line with that observed in historical lenalidomide studies (7-8%).

Second Primary Malignancies are known to be associated with lenalidomide exposure which was extended in patients treated with Empliciti combined with lenalidomide and dexamethasone vs. lenalidomide and dexamethasone. The rate of haematologic malignancies was the same between the two treatment arms. Patients should be monitored for the development of SPMs (SmPC section 4.4). Second Primary Malignancies have been classified as an important identified risk in the Risk Management Plan.

Hypersensitivity and anaphylactic reaction

Across all the completed elotuzumab studies a total of 2 subjects have been reported with the AE of anaphylaxis/anaphylactic reaction. In study CA204004, 9 subjects in the E-Ld arm reported an AE of hypersensitivity, and 4 subjects in the Ld arm reported an AE of hypersensitivity.

Cases of anaphylaxis were reported before the introduction of pre-medication. As anaphylaxis has a different underlying mechanism to what are known as standard infusion reactions, hypersensitivity and anaphylactic reaction have been classified as an important potential risk.

Age

In general, the safety profile of elotuzumab was similar between different age groups <65; ≥65 and <75; and ≥75 years of age in the E-Ld study, except for a higher frequency of SPMs in patients ≥65 years (n=18) compared with patients <65 (n=4) in the E-Ld arm. This imbalance was not observed in the LD arm, and might be caused by an imbalance in prior melphalan-containing regimens. Apart from one patient treated with E-Ld in study CA204004, there are no data on patients aged ≥85 years.

Renal Impairment

In renal impairment study CA204007, the frequency of SAEs and IRs was higher for SRI (n=9) and ESRD (n=9) patients compared to patients with a normal renal function and the percentage of AEs and Grade 3-4 AEs were balanced between the three subgroups. It can be taken into consideration that patients with severe renal disease are likely to have more advanced myeloma and may be more likely to suffer adverse events. Also the numbers are small, hampering interpretation of safety results. No clinically important differences in the pharmacokinetics of elotuzumab were found between patients with severe renal impairment (with and without dialysis) and patients with normal renal function (SmPC section 5.2) and no dose adjustment of Empliciti is required for patients with mild (CrCl = 60 89 mL/min), moderate (CrCl = 30 59 mL/min), severe (CrCl < 30 mL/min) renal impairment or end stage renal disease requiring dialysis (SmPC section 4.2).

Hepatic Impairment

No patients with moderate or severe hepatic impairment have been included in elotuzumab studies. Thus, data about safety in patients with moderate and severe hepatic impairment is missing. This has been adequately reflected in the SmPC (see section 4.2, and 5.2) and is reflected in the Risk Management Plan.

Safety in patients of Asian race

In study CA204004, approximately 10% of subjects were of Asian race. Although safety by race subgroup analysis did not reveal any clinically meaningful differences by race, the number of subjects with Asian race was low and therefore safety in patients of Asian race has been added as missing information to the Risk Management Plan. More data on safety of administration in Asian population is expected after market authorization of Empliciti.

Long term safety data

No new safety concerns were identified in patients treated with E-Ld for > 24 months. However, updated safety data was requested and provided by the Applicant for studies CA204004 (additional 6 months of data since the initial MAA; database lock date 15 May 2015) and CA204009 (additional 7 months of data since the initial MAA) to better characterize the long-term safety profile of E-Ld. Based on this data, despite a longer duration of treatment and follow-up, AE frequencies remained substantially similar compared to those presented in the initial MAA.

Effects on ability to drive and use machines

On the basis of reported adverse reactions, Empliciti is not expected to influence the ability to drive or use machines. Patients experiencing infusion reactions should be advised not to drive and use machines until symptoms abate (SmPC section 4.7).

Overdose

One patient was reported to be overdosed with 23.3 mg/kg of elotuzumab in combination with lenalidomide and dexamethasone. The patient had no symptoms, did not require any treatment for the overdose, and was able to continue on elotuzumab therapy. In clinical studies, approximately 78 patients were evaluated with elotuzumab at 20 mg/kg without apparent toxic effects. In case of overdose, patients

should be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted (SmPC section 4.9).

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics (SmPC, section 4.8).

2.6.2. Conclusions on the clinical safety

The safety profile of elotuzumab when administered in the proposed therapeutic dose in combination with the Ld regimen does not appear to diverge from what expected based on the mechanism of action of the mAb and is generally manageable.

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	Infusion reaction Infections 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 plan

The PRAC, having considered the data submitted, was of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

The PRAC also considered that routine pharmacovigilance is sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Infusion reaction Infections Second primary malignancies	SmPC warns of risk of infusion reaction, infection, and second primary malignancies Mandatory premedication for prevention of infusion reaction is included in section 4.2 of the SmPC as follows:	None.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Patients must receive premedication consisting of dexamethasone, H1 blocker, H2 blocker, and paracetamol administered prior to elotuzumab infusion. The following premedication must be administered 45 - 90 minutes prior to Empliciti infusion: • Dexamethasone 8 mg intravenous • H1 blocker: diphenhydramine (25- 50 mg orally once daily or intravenous) or equivalent H1 blocker. • H2 blocker: ranitidine (50 mg intravenous or 150 mg orally) or equivalent H2 blocker. • Paracetamol/ Acetaminophen (650 - 1000 mg orally).	
Hypersensitivity and anaphylactic reaction	Not applicable.	None.
Safety in patients with moderate and severe hepatic impairment	Not applicable.	None.
Safety in patients of Asian race	More data on safety of administration in Asian population is expected after market authorization of Empliciti.	None.

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indications.

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.1 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Empliciti (ELOTUZUMAB) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

To support the current application, two pivotal efficacy trials have been submitted. One was a phase 3, randomized, open-label study (CA204004) investigating the use of elotuzumab in combination with lenalidomide, (n=321), compared to Ld alone (n=325). The other was a Phase 2, open-label, randomized study (CA204009) of elotuzumab with bortezomib (n=77), compared to Bd alone (n=75), planned as a proof-of-concept study. The Applicant originally sought marketing authorization for the treatment of multiple myeloma (MM) as combination therapy in patients who have received one or more prior therapies but has modified this to limit the indication to the combination with lenalidomide and dexamethasone in the treatment of multiple myeloma in adult patients who have received at least one prior therapy.

Benefits

Beneficial effects

The results of the CA204004 study, showed a statistically significant improvement in the co-primary endpoint of PFS for elotuzumab plus lenalidomide compared with lenalidomide alone(HR 0.68, 97.61% CI 0.55, 0.83, p=0.0001) with a gain in median PFS of 4.2 months in favour of elotuzumab (18.5 months E-Ld vs. 14.3 months Ld). The PFS results were consistent across the majority of subgroups analysed with patients who were lenalidomide-experienced, had del17p or t(4;14) high risk cytogenetics at baseline, and patients ≥65 years of age demonstrating PFS improvement with elotuzumab. An objective response rate (co-primary endpoint) of 78.5% E-Ld vs 65.5% in the Ld group, with a common odds ratio of 1.94 supported the PFS results.

Regarding the secondary variables the use of the combination of elotuzumab provides a positive benefit in terms of OS (43.7 months for E-Ld versus 39.6 months for Ld), median duration of response (20.7 months for E-Ld versus 16.6 months for Ld group) and median TTNT (HR 0.62, 95%CI 0.49; 0.78).

Uncertainty in the knowledge about the beneficial effects

Only one patient with >3 prior treatment lines was included in the study CA204004 which remains an uncertainty in the knowledge of the population who are likely to benefit from Empliciti. Only 6% of

patients in study CA204004 had received prior lenalidomide treatment and no patients were refractory to lenalidomide and these uncertainties related to prior lenalidomide are mentioned in SmPC section 5.1.

The benefit in ORR with E-Ld treatment was mostly obtained by a higher frequency of partial responses and very good partial responses. However, surprisingly, the number of complete responses was higher in the Ld arm (1.6% E-Ld vs. 5.8 Ld). This may be due to cross-interference detection of in the SPEP (serum protein electrophoresis) and SIFE (serum immunofixation electrophoresis) assays testing M protein levels. It is most relevant where a qualitative assessment of an M-protein peak using serum immunofixation electrophoresis (SIFE) is involved in the response assessment and could potentially have affected a minority of subjects (15%) in E-Ld study CA204004. This has been adequately reflected in the SmPC (see section 4.5).

Risks

Unfavourable effects

Almost all patients in elotuzumab and control arm experienced an adverse event (AE). Higher frequencies of grade 3-4 AEs (78% E-Ld vs 66% Ld) , and serious AEs (65% E-Ld vs. 56% Ld;) were observed with the addition of elotuzumab to Ld.

The frequency of discontinuation due to study drug toxicity (all study drugs) was similar between the elotuzumab and control arm. Two patients discontinued study therapy with elotuzumab due to an infusion reaction.

In the E-Ld arm, similar relative dose intensity was observed for lenalidomide and dexamethasone in both treatment arms. Haematological grade 3-4 AEs were most prominent (primarily lymphopenia and leukopenia).

A higher rate of Any Grade and Grade 3-4 deep vein thrombosis was observed in E-Ld group compared with Ld group (Any Grade: 7.2% vs. 3.8%; Grade 3-4: 5.7% vs. 2.2%). Grade 3-4 SAEs were observed >10% more frequent in the elotuzumab arm compared with Ld (48.1% E-Ld vs 36.6% Ld). With pneumonia being the most frequent reported Grade 3-4 SAE.

Overall, more deaths (mostly due to disease progression) were observed in the control arm compared with the elotuzumab arm. However, more patients died due to infection in the E-Ld arm compared with the Ld arm (2.2%, n=7 E-Ld vs. 0.6%, n=2 Ld). Of these infections, 4 in the E-Ld arm, and none in the Ld arm were related to the pulmonary tract. Apart from an increase in deaths due to infection in the E-Ld arm, a higher frequency of infection AEs (81% vs. 74%), grade 3-4 AEs (28% vs. 24%) and SAEs of infection (31% vs 25%) was observed compared with the Ld arm.

Infusion reactions (IRs) occurred in approximately 10% of elotuzumab treated patients. They were usually mild to moderate and manageable using recommended guidelines for premedication.

The addition of elotuzumab to lenalidomide did slightly increase the occurrence of secondary primary malignancies (SPMs; 6.9% E-Ld vs 4.1% Ld), even when corrected for exposure duration.

In general, the safety profile of elotuzumab was similar between different age groups <65; ≥65 and <75; and ≥75 years of age in the E-Ld study, except for a higher frequency of SPMs in patients ≥65 years (n=18) compared with patients <65 (n=4) in the E-Ld arm.

In renal impairment study CA204007, the frequency of SAEs and IRs was higher for patients with severe renal impairment (SRI) and end stage renal disease (ESRD) compared to patients with a normal renal function.

Uncertainty in the knowledge about the unfavourable effects

A higher frequency of AEs, SAEs and deaths due to infection was observed in the E-Ld arm of study Ca204004 compared to the Ld arm, indicating that infection is an important, and potentially fatal, identified risk. Despite a higher frequency of grade 3-4 lymphopenia detected with elotuzumab treatment (12-28% more frequent compared to control arms), this did not translate into a higher rate of infections. However, no measurable factor or characteristic was identified in the elotuzumab-treated population that could predict susceptibility to an infection. Most of the measurable factors were similar between the two study cohorts.

With the exception of Herpes zoster, the rates of opportunistic infections were similar between E-Ld and Ld. Additional data showed that subjects with prophylactic therapy had a lower frequency of infection than those without prophylactic anti-infective therapy in both treatment arms, although the differences are small. There was also a reduction in the frequency of Grade 3-4 infections in both arms. It is acknowledged that these data could be confounded given that prophylaxis was not mandatory, and subjects at highest risk for infection were given antibacterial and/or antivirals. This safety concern is addressed in section 4.4 of the SmPC and infections have been classified as an important identified risk in the Risk Management Plan.

Data on the efficacy and safety of Elotuzumab in patients $\geqslant$ 85 years of age are very limited. This has been reflected in section 4.2 of the SmPC.

Although no safety concerns seem to arise from immunogenicity data, considering that IRs are a recognized risk with Elotuzumab, and may be related with ADAs, more data were submitted. These data showed that, overall, the incidence of IRs among subjects with on-study ADA and persistent ADA is higher in the CA204004 study. It is acknowledged that the small numbers prevent from drawing definite conclusions on the interpretation of the relationship between IR and ADA. No substantial subset of patients with a higher risk of IR could be identified in study CA204004.

Effects Table

Table 48. Effects Table for Empliciti in relapsed/refractory MM (data cut-off study CA204004: 4 November 2014)

Effect	Short Description	Unit	Treatment (E-Ld)	Control (Ld)	Uncertainties/ Strength of evidence	References
Favourable Effects						
PFS	Time from randomization until PD or death due to any cause	Months (KM median; 95% CI)	18.5 (16.5, 21.4) HR of 0.68 (95% CI 0.56, 0.83; p = 0.0001)	14.3 (12.0, 16.0)	Primary endpoints met - PFS supported by ORR and OS but not by complete responses and QoL endpoints - No pts refractory to prior lenalidomide or and only 1 pt with >3 prior regimens included	See clinical efficacy AR and discussion
ORR	The proportion of patients who have either PR or CR using EBMT criteria per IRC	Percentage (95% CI)	78.5% (73.6, 82.9) Common Odds Ratio 1.94 (95% CI 1.36, 2.77, p=0.0002)	65.5% (60.1, 70.7)		
OS preliminary	Time from randomization to death due to any cause	Months (KM median; 95% CI)	43.7 40.34, NE)	39.6 (33.25, NE)		
Unfavourable Effects						

Effect	Short Description	Unit	Treatment (E-Ld)	Control (Ld)	Uncertainties/ Strength of evidence	References
AEs (e.g. fatigue, diarrhea, pyrexia, constipation, cough;	Incidence as percentage of patients involved	Percentage (%)	Grade 3-4 AEs: 77.7%	Grade 3-4 AEs: 65.6%	- A higher frequency of AEs, SAEs and deaths due to infection was observed. Unknown whether pts at risk can be identified.	See clinical safety AR and discussion.
SAEs (>3% e.g. pneumonia, pyrexia, pulmonary embolism, respiratory tract infections, cellulitis, diarrhoea, syncope)	Incidence as percentage of patients involved	Percentage (%)	65.4%	56.5%	- Safety profile in pts >85 years of age is unknown. - The incidence of IRs among subjects with ADA is higher than in ADA negative subjects.	

Abbreviations: AE: adverse event, ADA; anti-drug antibodies, B: bortezomib, CI: confidence interval, CR: complete response, d: dexamethasone, E: elotuzumab, INV: investigator, IRC: independent review committee, KM: Kaplan Meier, L: lenalidomide, ORR: overall response rate, OS: overall survival, PFS: progression free survival, PR: partial response, pts: patients, SAE: serious adverse event, SCT: stem cell transplant.

Benefit-risk balance

Importance of favourable and unfavourable effects

Most of the population investigated had had one or two prior therapies, and would be expected to still have other treatment options. However, the availability of a new treatment with a new mechanism of action and manageable adverse event profile is of importance in the treatment of MM which is characterised by relapse to successive therapies with an unmet medical need.

In the pivotal E-Ld study a median PFS benefit of 4.2 months has been demonstrated for E-Ld (18.5 months E-Ld vs. 14.3 months Ld) in the ITT analysis. A PFS improvement of this size is of clinical relevance in these previously treated patients of whom 36% and 16% had had 2 or 3 prior lines of therapy respectively and of whom 35% were refractory to their last prior therapy. This was supported by favourable Time To Next Treatment data (HR 0.62, 95%CI 0.49; 0.78) and by an ORR benefit for the E-Ld combination with a rate of 78.5% for E-Ld compared to 65.5% for Ld, also of clinical relevance. However, the pain score and QoL endpoints in the E-Ld study did not show a difference between the two treatment arms.

There appears to be a trend towards improved OS for E-Ld with higher survival rates compared to Ld at 1 and 2 years, but survival data are immature and a benefit in OS cannot be concluded.

The safety profile of elotuzumab when administered in the proposed therapeutic dose in combination with the Ld regimen does not appear to diverge from what expected based on the mechanism of action of the mAb. The safety profile of the E-Bd combination does not seem to differ significantly, in terms of type of AEs, from that observed for the combination of elotuzumab with Ld. Generally the adverse event profile, including infusion reactions, was manageable for both combinations and did not require support with growth factors or platelet / erythrocyte transfusions. Although adverse events did lead to discontinuation of study treatments in approximately 25% to 30% of patients, in the pivotal studies for both E-Ld and E-Bd the rate of these discontinuations was not higher in the elotuzumab arms compared to the comparator arms.

Benefit-risk balance

For the E-Ld combination a relevant improvement in PFS is considered to be present, supported by (preliminary) OS data and improvement in ORR.

Safety appears manageable, although in particular infections remain a point of concern. In view of the effect in terms of PFS and ORR, the coherent evidence from secondary efficacy endpoints and the lack of significant uncertainty in terms of efficacy or safety, the toxicity profile is considered acceptable.

The benefit-risk balance for elotuzumab for the treatment of multiple myeloma in adult patients who have received at least one prior therapy is considered positive.

Discussion on the benefit-risk balance

Efficacy of E-Ld was maintained in patients with up to 3 prior lines of therapy, the population studied in study CA204004. In patients treated with E-Ld, the median PFS was similar in patients with 1, 2 or 3 prior lines of therapy. Median overall survival was similar in patients with 1 or 2 prior lines of therapy and somewhat lower in those with 3 prior lines. Importantly, the benefit in PFS and in OS compared to Ld increased in those with 3 prior lines, justifying it's use in those with more advanced disease. Also in patients with refractory disease, there was clear median PFS benefit of approximately 6 months.

In patients with lower risk disease, specifically patients not refactory to prior treatment and those in IMWG standard risk category, PFS benefit was also evident. The median PFS benefit of E-Ld compared to Ld was approximately 3 months, approximately 1 month less than in the overall population.

In patients who had not had prior IMiD therapy (no lenalidomide or thalidomide) the PFS benefit of E-Ld compared to Ld (approximately 1.4 months) was lower than in the overall population and was higher in patients who had received prior thalidomide therapy (approximately 6 months). However, the thalidomide-exposed population, which represented approximately 50% of included patients, is likely to be very heterogeneous with regard to the nature and extent of the prior thalidomide therapy. It cannot be excluded that the higher efficacy observed in the IMiD exposed population (principally thalidomide exposed as only 6% of patients had prior lenalidomide exposure) might have been driven by patients with long-term exposure or who have become refractory to thalidomide.

Information is included in SmPC Section 5.1 on the PFS and HR in the subgroups of those who had prior IMiD (Thal) and no prior IMiD, refractory and not refractory patients, and those with high risk and standard risk MM.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Empliciti is not similar to Thalidomide Celgene, Revlimid, Imnovid, Farydak and Kyprolis within the meaning of Article 3 of Commission Regulation (EC) No. 847/200 (see Appendix 1).

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Empliciti indicated in combination with lenalidomide and dexamethasone for the treatment of multiple myeloma in adult patients who have received at least one prior therapy is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that elotuzumab is qualified as a new active substance.