CLINICAL STUDY PROTOCOL

Phase 2 study of carfilzomib + elotuzumab + dexamethasone for relapsed or progressed multiple myeloma after 1-3 prior treatment lines

Indication: **Relapsed or progressed multiple myeloma**
Phase: **Phase 2**

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Principal Investigator signature page

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Date

By my signature, I agree to personally supervise the conduct of this study and to ensure its conduct in compliance with the protocol, informed consent, IRB/EC procedures, the Declaration of Helsinki, ICH Good Clinical Practices guideline, the EU directive Good Clinical Practice, and local regulations governing the conduct of clinical studies.

Study Title: Phase 2 study carfilzomib + elotuzumab + dexamethasone for relapsed or progressed multiple myeloma patients after 1-3 prior treatment lines

Phase: Phase 2

Number of Patients: 40

Study Objective: To investigate the safety and feasibility of carfilzomib + elotuzumab + dexamethasone combination and initial efficacy in relapsed or progressed multiple myeloma patients

Study Endpoints

Primary

- Overall response rate (ORR) with carfilzomib + elotuzumab + dexamethasone

Secondary

Complete response rate (CR)

- Quality of response (proportion of minimal residual disease (MRD) negativity in patients with at least VGPR response)
- Duration of responses
- Progression-free survival (PFS)
- Time to next treatment (TTNT)
- Safety (Adverse events)

Overview of Study Design:

This Nordic Myeloma Study Group study is a phase 2 study for advanced MM patients below 75 years of age. The main aim of this study is to assess the ORR with a new drug combination, carfilzomib + elotuzumab + dexamethasone (CAR-ELO-Dex). Even if this is not a randomized study rough comparisons can be done with earlier reports of different regimens in the same clinical situation. In addition, safety assessment is of critical importance for a new regimen. A modern concept is to study the depth of CR responses with a sensitive multiparameter flow cytometry (MFC) method for MRD assessment – an endpoint that is mostly lacking in previous studies for this patient population. We assume that treatment with this new combination of CAR + ELO + Dex will produce at least as good responses as the most efficient regimens so far used in this clinical situation, and there will be a substantial proportion of CR responses with MRD-negativity which can be regarded as an indicator of high-level treatment efficacy and which gives a good basis for comparisons of treatment efficacy between different study regimens in future.

The target population of the study is the patients who have relapsed or progressed after 1 to 3 prior treatment lines in which PI (bortezomib and/or ixazomib) and/or lenalidomide have

been included. The primary endpoint is overall response rate (ORR) while the secondary endpoints include complete remission (CR), duration of response, assessment of the depth (quality) of CR with MRD measurement by flow cytometry, estimation of PFS and time to next treatment, and evaluation of adverse events and safety.

The cycle length is 28 days.
The ELO dose is 10 mg/kg in all cycles.
CAR dose is initially (Cycle 1, day 1) 20 mg/m^2 weekly after which it will be increased to 56 mg/m^2 weekly in the first 5 patients in the first two cycles. If no safety problems occur the dose is increased to 70 mg/m^2 weekly for the rest of the study, and the patients after the first 5 patients will receive this dose right after the initial weekly dose of 20 mg/m^2
Dexamethasone dose is 40 mg weekly throughout the study.

Drug administration schedule:

Cycles 1-2

CAR and ELO are administrated at weekly intervals on cycle days 1, 8 and 15.
Dexamethasone will be given on days 1, 8, 15 and 22.

Cycles 3-8

CAR will be administered similarly as in cycles 1-2.
ELO will be given on cycle days 1 and 15.
Dexamethasone as in cycles 1-2.

Cycles 9 -

CAR, ELO and Dex will be given on days 1 and 15 from cycle 9 until relapse or progression or excess toxicity.

Duration of Study:

Expected duration of treatment:

- patient recruitment 24 months
- primary endpoint (ORR) together with the relevant secondary endpoints will be assessed after the minimum follow-up of one year has been reached with the last included patient
- to assess PFS and TTNT all patients will be followed until 4 years after first dose

LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Common abbreviations used in oncology protocols are provided below. Program-specific or protocol-specific abbreviations must be added to this list, and unnecessary abbreviations removed, as applicable. Abbreviations that are retained should not be changed.

Abbreviation	Term
AE	adverse event
AFOS	alkaline phosphatase
ALT, ALAT	alanine aminotransferase
ANC	absolute neutrophil count
API	active pharmaceutical ingredient
ASCO	American Society of Clinical Oncology
ASCT	Autologous stem cell transplantation
ASO-RQ	Allele specific oligonucleotide real-time quantification
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
$AUC_{24\ hr}$	area under the plasma concentration versus time curve from zero to 24 hours
AUC_{inf}	area under the plasma concentration versus time curve from zero to infinity
AUC_{τ}	area under the plasma concentration versus time curve from zero to next dose
BID	bis in die; twice a day
BM	bone marrow
BSA	body surface area
BUN	blood urea nitrogen
BZM	Bortezomib
CBC	complete blood count
CL	clearance, IV dosing
CL_P	plasma clearance
CL_{Total}	total clearance
C_{max}	single-dose maximum (peak) concentration
CNS	central nervous system
CR	complete remission
CrCl	Creatinine Clearance
CRO	Clinical trial research organization
CRP	C-reactive protein
CT	computed tomography

Abbreviation	Term
CY	Cyclophosphamide
CYP	cytochrome P_{450}
DDI	drug-drug interaction
DLT	dose-limiting toxicity
DME	drug metabolizing enzymes
DNA	deoxyribonucleic acid
DSRT	Drug sensitivity and resistance testing
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
EU	European Union
FDA	United States Food and Drug Administration
FISH	Fluorescence in situ hybridization
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
GFR	Glomerular filtration rate
GI	Gastrointestinal
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practice
Hb	Hemoglobin
Hct	Hematocrit
HDT	High-dose treatment
HIV	human immunodeficiency virus
HR	High-risk
IB	Investigator's Brochure
IC_{50}	concentration producing 50% inhibition
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IMiD	Immunomodulatory drug
IMWG	International Myeloma Working Group
IRB	institutional review board

Abbreviation	Term
ITT	intent-to-treat
IV	intravenous; intravenously
KPS	Karnofsky Performance Status
LDH, LD	lactate dehydrogenase
LR	Low-risk
MDS	Myelodysplasia
MedDRA	Medical Dictionary for Regulatory Activities
MFC	Multiparameter flow cytometry
Millennium	Millennium Pharmaceuticals, Inc., and its affiliates
MM	Multiple myeloma
MR	Minimal response
MRI	magnetic resonance imaging
MRD	Minimal residual disease
MTD	maximum tolerated dose
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NDMM	Newly diagnosed multiple myeloma
NGS	Next generation sequencing
NMSG	Nordic Myeloma Study Group
nCR	Near complete remission
NYHA	New York Heart Association
ORR	Overall response rate
OS	Overall survival
PCR	polymerase chain reaction
PD	Progressive disease
PFS	Progression-free survival
PB	Peripheral blood
Pgp	P-glycoprotein
PI	Proteasome inhibitor
PK	pharmacokinetic(s)
PO	*per os*; by mouth (orally)
PR	partial remission
PRO	patient-reported outcome

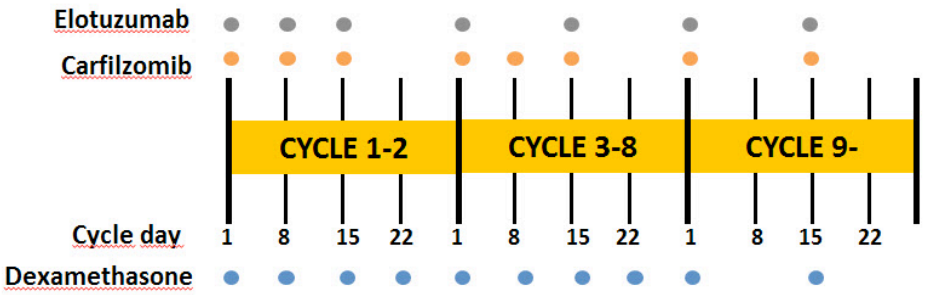
Abbreviation	Term
QD	*quaque die*; each day; once daily
QID	*quater in die;* 4 times a day
QOD	*quaque altera die*; every other day
QOL	quality of life
RNA	Ribonucleic acid
RRMM	Relapsed/refractory multiple myeloma
SAE	serious adverse event
SC	Subcutaneous
sCR	Stringent complete remission
SD	stable disease
SJS	Stevens-Johnson syndrome
SmPC	Summary of Product Characteristics
SPM	Second primary malignancy
SR	Standard-risk
$t_{1/2}$	terminal disposition half-life
TEN	Toxic epidermal necrolysis
TFR	Tumor flare reaction
T_{max}	single-dose time to reach maximum (peak) concentration
TTNT	Time to next treatment
UK	United Kingdom
ULN	upper limit of the normal range
US	United States
VGPR	Very good partial remission
VTE	Venous tromboembolism
WBC	white blood cell
WHO	World Health Organization

Table 1. Schedule of study investigations

	Screening	Cycles 1- until end of study, D1 (lab within 5 days before)	Cycles 1-8, D8 D15, D22* (lab within 3 days)	Cycles 1-8 D15	Cycles 9-, D15 until end of study (lab in 3days)	End of study
Medical history	X					
Physical examination + neurol.evaluation	X	X	X**			X
Vital signs	X	X	X*		X	X
Hematology	X	X				X
Immunochemistry	X	X				X
Blood chemistry	X	X				X
Pvk+neut+tromb, K,Na,krea,alat, afos,bil (safety lab*)			X*		X	
Safety assessment, AEs	X	X	X*		X	X
BM aspiration+ 8-color EuroFlow	X		X (when VGPR has achieved, repeated if VGPR/CR and after 1 year if VGPR/CR)			
Bm-MM-FISH	X					
Bone imaging	X					
ECG (a)	X					
Thorax x-ray	X					
Cardiac ECHO	X					
Biobank	X			In CR and at relapse		
Samples to FIMM in Finland	Finland			Bm + blood at relapse		
Pregnancy test (b)	X	X (b)				
Quality of Life		X		X		X

a) ECG in C1-2, D1, thereafter if clinically needed. b) Pregnancy testing must be performed at the beginning of each 28-day cycle and at the end of study visit, applying to women of childbearing potential. * Vital signs not needed on D22 and after C2 Safety lab and AEs on D22 if clinically needed. ** Physical examination if needed due to clinical symptoms.

Table 2. Study schema



1. INTRODUCTION

1.1 Scientific background

Multiple myeloma (MM) is the most common hematological malignancy after lymphomas. In years 2009-2013, 955 male and 781 female new myeloma patients per year have been registered in the Nordic Cancer Registries (NORDCAN) giving an incidence of 4-6/100 000 per year (Engholm et al.2015). Multiple myeloma is considered as an incurable disease. The overall survival (OS) of patients has doubled in the last 30 years from a median of 2−3 years to 4−6 years in elderly patients, and up to 8−10 years for younger patients, due to autologous stem cell transplantation (ASCT) combined with immunomodulatory drugs and proteasome inhibitors. The International Myeloma Working Group (IMWG) recently proposed new risk stratification standards for MM patients: high-risk (HR), standard-risk (SR) and low-risk (LR) groups, t(4;14) and del(17p) indicating the worst prognosis among cytogenetic aberrations. Although a median OS of LR patients is > 10 years from diagnosis, new drugs and therapeutic innovations are urgently needed for HR patients with a median OS of only two years (Chng et al. 2014). High-dose therapy supported by ASCT is the standard first-line therapy for MM in eligible patients under 65 (-70) years.

The general consensus for induction treatment is a triple combination of proteasome inhibitor (PI) plus immunomodulatory, alkylating agent or doxorubicin with dexamethasone for 3-4 cycles. Of the second generation PIs intravenously used carfilzomib has been approved by FDA and EU for MM, and elotuzumab so far by FDA, in the setting of relapsed/refractory myeloma. All patients relapse after first-line therapy, and there may be several relapses in the course of the disease. The treatment of relapses and progression in successive treatment-lines is a challenge and has a significant impact on overall survival. In the fight against final refractoriness of the disease new and more effective drugs and their combinations are needed. Monoclonal antibody against myeloma cell together with proteasome inhibitor and/or immunomodulatory drug offers a tempting basis for an effective combination regimen.

1.2 Relapsed myeloma

1.2.1 Definition of relapse

According to the consensus recommendations for the uniform reporting of clinical trials by IMWG relapsed myeloma is defined as previously treated myeloma that progresses and requires initiation of salvage therapy but does not meet criteria for either "primary refractory myeloma" or "relapsed-and-refractory myeloma" categories. Relapsed and refractory myeloma is defined as disease that is nonresponsive while on salvage therapy, or progresses within 60 days off last therapy in patients who have achieved MR or better. Primary refractory myeloma is defined as a nonresponsive disease in patients who never have achieved a minimal response or better with any therapy (Rajkumar et al. 2011). In characterization of study populations it is essential to differentiate between these categories. Otherwise it is hard to make any comparisons between different studies.

1.2.2 Relapse treatment

The length of survival depends in addition to the successful first-line treatment on the efficacy of the treatment of relapse and progressive phases. Thus, the patient may have many treatment lines, and usually the response duration will shorten after each successive regimen (Kumar et al. Mayo Clin Proc 2004; 79:867-74). Many different drugs and their combinations have been used but there is no consensus about the recommended treatment strategy for relapsed and progressive disease. In general, if relapse occurs more than 6-9 months after the end of the previous regimen, the same regimen is worth trying again. Similarly, autologous stem cell transplantation can be performed as a salvage treatment if the PFS-1 has been at least 12-18 months. An aggressive relapse may benefit of the most aggressive treatment regimen. (Rajkumar SV. AmJHematol 2016;91:90-100). Figures of responses and PFS for the most recent randomized studies in relapsed myeloma are shown below (Rajkumar SV. AmJHematol 2016).

TABLE 3. Results from recent large randomized studies in relapsed multiple myeloma (modified from Rajkumar et al 2016).

Author	Regimen	No patients	ORR (%)	CR (%)	PFS (mo)	*P* for PFS
San Miguel et al 2013	PomDex Dex	302 153	31 10	1 0	4.0 1.9	<0.0001
Stewart et al 2015	KRd Rd	396 396	87 67	32 14	26.3 17.6	0.0001
Dimopoulos et al 2016	KDex VDex	464 465	77 63	13 6	18.7 9.4	<0.0001
San Miguel et al 2014	Pano-Vd Vd	387 381	61 55	11 6	12 8.1	<0.0001
Lonial et al 2015	Elo-Rd Rd	321 325	79 66	4 7	19.4 14.9	<0.001
Moreau et al 2015	IRd Rd	360 362	78 72	12 7	20.6 14.7	0.012

The highest ORR rates have varied between 78-87 % and the respective CR rates between 4 and 32 % (Table 3). When looking results from the two studies comparing KRd to Rd and EloRd to Rd it seems that in spite of comparable ORR rates carfilzomib may produce higher CR rates than elotuzumab when combined with Len and Dex. The importance of achieving CR for PFS and OS has been shown in the first-line setting in a meta-analysis. Moreover, several studies have demonstrated also the correlation between low or negative minimal residual disease (MRD) and improved outcome in MM, and in recent years several publications have confirmed the impact of MRD-negative status for long-term outcome. FDA has considered to accept the MRD as a new criteria for assessing outcome in addition to PFS and OS.

We may assume that combining elotuzumab and carfilzomib is a feasible study protocol design and may well produce higher CR rates than elotuzumab plus lenalidomide. MRD status has usually not been used in the response analyses, and this aspect will strengthen the value of efficacy assessment of CAR+ELO combination and may allow comparisons to other regimens in future.

1.3 Minimal residual disease measurement

Both allele specific real-time quantitative polymerase chain reaction (ASO RQ-PCR), multiparameter flow cytometry (MFC) and next generation sequencing (NGS) have been used in MM to assess MRD. The MFC and ASO RQ-PCR have been compared with NGS assay for MRD assessment and NGS seems to be most sensitive bypassing the technical problems related to designing the PCR probe, but this has to be confirmed (Paiva et al.2015). To standardize the MFC method after the first paper of Rawstron et al. EuroFlow Consortium has published the guidelines for MFC for diagnostic panel in plasma cell disease (Stetler-Stevenson et al.2016). The consensus guidelines for MFC-MRD sample processing and MRD detection have now been published (Rawstron et al. 2016). In practice MFC is the most practical and fastest method for MRD assessment.

1.4 STUDY DRUGS

1.4.1 Elotuzumab

Elotuzumab (BMS-901608, HuLuc63) is an immunostimulatory humanized, IgG1 monoclonal antibody that specifically targets the SLAMF7 (Signaling Lymphocytic Activation Molecule Family member 7), a cell surface glycoprotein. SLAMF7 is highly expressed on myeloma cells independent of cytogenetic abnormalities. SLAMF7 is also expressed on Natural Killer cells, plasma cells and at significantly lower levels on specific immune cell subsets, but is not detected on normal solid tissues or hematopoietic stem cells. 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). Elotuzumab demonstrates a dual mechanism that includes: 1) direct NK cell activation and 2) NK cell-mediated ADCC. Elotuzumab can also kill MM cell lines in vitro in the presence of peripheral blood mononuclear cells (PBMCs) or

purified NK cells. Because of its potent antitumor activity, elotuzumab is being developed as a clinical candidate for the treatment of MM. In preclinical models, elotuzumab has demonstrated synergistic activity when combined with lenalidomide or bortezomib.

Phase 1 and 2 studies have been conducted to evaluate the pharmacokinetics (PK), safety, and preliminary efficacy of elotuzumab. The Phase 3 dose of 10 mg/kg was selected based on the safety, efficacy, PK, and SLAMF7 saturation results in these studies. Although the clinical results with elotuzumab monotherapy have been only modest, i.e. stable disease as the best response, phase 1-2 combination trials have resulted in more than 80 % ORR (at least PR) in relapsed patients and prolonged PFS as well. The first 3 trials (HuLuc63-1701, HuLuc63-1702, and HuLuc63-1703) were Phase 1 studies in relapsed MM subjects with elotuzumab as monotherapy or combined with bortezomib or lenalidomide, respectively. Results of the monotherapy Phase 1 trial (HuLuc63-1701) demonstrated acceptable safety with no maximum tolerated dose (MTD) identified up to 20 mg/kg. Stable disease was reported for 27% of the 35 subjects treated with elotuzumab monotherapy. Data from HuLuc63-1702 (combination with bortezomib/dexamethasone) demonstrated adequate safety, with no MTD observed up to 20 mg/kg and an objective response rate (ORR) of 48% among 28 subjects. Data from the Phase 1 portion of HuLuc63-1703 (combination with lenalidomide/dexamethasone) demonstrated acceptable safety, with no MTD observed up to 20 mg/kg and an ORR of 82% among the 28 evaluable subjects. The HuLuc63-1703 trial also included a Phase 2 portion that demonstrated an ORR of 84% among all 73 treated subjects. Median progression-free survival (PFS) was 29 months. The most common adverse events (AEs) were diarrhea, muscle spasms, fatigue, and constipation. The key elotuzumab-related events have been infusion-related AEs in all studies. Infusion reactions have been mitigated with premedications consisting of corticosteroids, H1 and H2 antagonists, and acetaminophen.

Across two randomized studies (CA204004, CA204009), elotuzumab combined with lenalidomide or bortezomib demonstrated compelling evidence of benefit as measured by clinically meaningful improvements in progression free survival, response rate, durability of response and trend in overall survival. The CA204004 and CA204009 trial demonstrate that elotuzumab 10 mg/kg combined with standard of care therapy results in a clinically meaningful median PFS of 19.4 and 9.7 months compared to significantly shorter PFS with Ld or Bd treatment, respectively. More importantly, a proportion of subjects experience a prolonged benefit as evidence by a 1 and 2-year PFS rate of 68%/48% for E-Ld and 1 year PFS rate of 39% for E-Bd. The improvement in ORR is bolstered by the median durability of 20.7 and 10.3 months for E-Ld and E-Bd, respectively. Finally, the preliminary trend in overall survival favoring elotuzumab treatment was consistently observed with E-Ld with 1 and 2-year OS rates of 91%/74% and a 1 year OS of 85% with E-Bd.

Elotuzumab has an acceptable and manageable safety profile in relapsed or refractory MM subjects. Minimal incremental AEs were reported beyond those associated with lenalidomide or bortezomib therapy, particularly evidenced by exposure adjusted event rates. Infusion reactions are mitigated with a standard premedication regimen and infusions of 10 mg/kg of elotuzumab up to 5 mL/min appear safe and tolerable. Elotuzumab's safety profile supports its use in long-term treatment, young and elderly patient population and in those with normal or impaired renal function.

Elotuzumab presents a novel, specific treatment for MM that engages the innate immune system through natural killer cells to specifically kill myeloma cells. Elotuzumab demonstrates a favorable benefit-risk profile in MM patients who have received one or more prior therapies in combination with Ld or Bd, nearly all of whom ultimately relapse and die with existing therapies. These results clinically validate the novel immunotherapeutic strategy of targeting SLAMF7 in this lethal hematologic malignancy. The randomized trials, CA204004 and

CA204009, provide compelling evidence that elotuzumab provides long-lasting therapeutic outcomes and represents an important approach to treating MM.

Clinical pharmacodynamics of elotuzumab

The relationship between SLAMF7 saturation on putative MM cells and elotuzumab levels in blood was assessed in all 3 Phase 1 studies using common markers that define MM cells (CD38 and CD138). More than 80% of the antigen-rich CD38+ putative myeloma cells at Study Day 56 (14 days after the last dose of elotuzumab) appeared to have fully occupied (i.e., saturated) SLAMF7 receptors when serum concentrations of elotuzumab reached between 10 and 100 mg/mL. Saturation of SLAMF7 by elotuzumab on bone marrow target cells increased as the dose of elotuzumab increased. At doses of 10 mg/kg and 20 mg/kg elotuzumab, SLAMF7 receptors on bone marrow-derived myeloma cells were consistently saturated. Lower dose groups exhibited more variation in the level of target cell saturation achieved.

Pharmacokinetics of elotuzumab

Safety pharmacology studies have not been conducted. Such studies were not considered relevant in view of the specificity of the interaction of elotuzumab with its target (ICH S6). In particular, elotuzumab is targeting a molecule/pathway that is not known to be involved in the functioning of the 3 main organ systems: central nervous system, respiratory system, and cardiovascular system. The population pharmacokinetics (PK) analysis suggested no difference in clearance of elotuzumab based on age, sex, race, baseline lactate dehydrogenase (LDH), albumin, β2-microglobulin, mild hepatic dysfunction, renal function (as measured by estimated glomerular filtration rate), and Eastern Cooperative Oncology Group (ECOG) performance status. Based on a population PK model, when elotuzumab is given in combination with lenalidomide and

dexamethasone, approximately 97% of the maximum steady-state concentration is predicted to be eliminated with a geometric mean of 82.4 days.

Geriatric Population

Of the 785 patients across treatment groups in Studies 1 and 2, 57% were ≥ 65 years of age; the number of patients ≥ 65 years was similar between treatment groups for either study. No overall differences in safety or efficacy were observed between patients ≥ 65 years and younger patients (< 65 years) in either study.

Renal Impairment

In a study evaluating elotuzumab in patients with renal impairment, the pharmacokinetics of elotuzumab in combination with lenalidomide and dexamethasone did not significantly differ between patients with normal renal function, severe renal impairment not requiring dialysis, or end-stage renal disease requiring dialysis. Dose adjustments of elotuzumab are not needed in patients with mild, moderate, severe renal impairment or end stage renal disease requiring dialysis.

Hepatic Impairment

Elotuzumab is an IgG1 monoclonal antibody, which is likely eliminated via several pathways similar to that of other antibodies. Hepatic excretion is not expected to play a dominant role in the excretion of elotuzumab. Based on a population pharmacokinetic analysis, no dose adjustment of elotuzumab is recommended for patients with mild hepatic impairment. Elotuzumab has not been studied in patients with moderate or severe hepatic impairment. Monitor liver enzymes periodically. Stop elotuzumab upon Grade 3 or higher elevation of

liver enzymes. After return to baseline values, continuation of treatment may be considered.

Elotuzumab up to 20 mg/kg did not have clinically meaningful effects on ECG parameters, including QTc interval.

1.4.1.1 Clinical safety and drug-related adverse events

Adverse events in elotuzumab (E) plus bortezomib (B) plus dexamethasone (d) study

Regarding present study with 2nd generation proteasome inhibitor (PI) CFZ combined with ELO and Dex, the most frequently reported AEs when elotuzumab has combined with 1st generation PI, BZM, and Dex were following:

Non-hematology Grade 3-4 events (≥5%) in the E-Bd group were diarrhea (8%), pneumonia (6.7%), hyperglycemia (12%), hypokalemia (5.3%), and peripheral neuropathy (8%). In the Bd group, the most frequently reported non-hematology Grade 3-4 events (≥5%) were pneumonia (6.7%), hyperglycemia (5.3%), peripheral neuropathy (9.3%), and paraesthesia (5.3%). Grade 3-4 AEs of infection were reported in 17.3% of the E-Bd and 13.3% of the Bd subjects. The most common Grade 3-4 AE of infection was pneumonia, (6.7% for both the E-Bd and Bd groups).

The most common Grade 3-4 SAE was pneumonia in both groups (6.7% subjects in E-Bd and 4% subjects in Bd). In the E-Bd group, infection was reported in 16 subjects (21.3%); Grade 3-4 infections were reported in 11 subjects (14.7%). Similar results were reported for subjects in the Bd group (12 total subjects [16%]; Grade 3-4 in 9 subjects [12%]).

The most common Grade 3-4 event leading to discontinuation (i.e., in ≥ 2 subjects) in the E-Bd group was thrombocytopenia (2 subjects [2.7%]) and diarrhea (2 subjects [2.7%]), and in the Bd group was pneumonia (3 subjects [4%]), peripheral neuropathy (3 subjects [4%]), paraesthesia (3 subjects [4%]), and orthostatic hypotension (2 subjects [2.7%]).

The primary cause of death in subjects was disease progression (14 subjects [18.7%] in E-Bd group and 16 subjects [21.3%] in Bd group). There was 1 study drug-related death.

In the pooled data from all ongoing elotuzumab studies the death rate was 0.7% (6 patients) by the IB 10 Aug 2015, version 11.

Most common adverse reactions by the 11/2015 Prescribing information: 20% or higher: Fatigue, diarrhea, pyrexia, constipation, cough, peripheral neuropathy, nasopharyngitis, upper respiratory tract infection, decreased appetite and pneumonia

Table 4. Adverse drug reactions with elotuzumab

Adverse drug reactions in patients treated with elotuzumab in clinical studies			
System organ class	**Preferred term**	**Overall frequency***	**Grade 3-4 frequency**
Infections and infestations	Herpes zoster	Common	Common
Blood and lymphatic system disorders	Lymphopenia, including decreased lymph-count	Very common	Very common
Immune system disorders	Hypersensitivity	Common	Uncommon
Psychiatric disorders	Mood altered	Common	
Nervous system disorders	Hypoaesthesia	Common	Uncommon
Respiratory, thoracic and mediastinal disorders	Cough, incl.productive cough and upper-airway cough syndrome	Very common	Uncommon
General disorders and administration site conditions	Chest pain	Common	Common
Investigations	Weight decreased	Very common	Uncommon
Injury, poisoning and procedural complications	Infusion related reaction	Common	Common
*Overall frequency includes reported serious and non-serious adverse drug reactions			

Infusion Reactions

Most biologics carry a risk for infusion reactions. Infusion reactions typically develop during the infusion or shortly thereafter, vary in symptom severity from mild to potentially life threatening and are commonly associated with a variety of signs and symptoms.

The mechanisms by which monoclonal antibodies elicit infusion reactions remain unclear.

- Monoclonal antibodies may interact with their molecular targets on circulating blood cells, tumor cells, or effector cells recruited to the tumor site (e.g., rituximab with CD20), thereby promoting the release of inflammatory cytokines.
- Infusion reactions may have a hypersensitivity component, in which the molecular structure of the drug or a component of the drug formulation is recognized as an antigen by the immune system. IgE mediated events are rare but possible
- Non-immune-mediated "hypersensitivities" are frequent following monoclonal or polyclonal antibody administration. This reaction resembles immune mediated reactions but an immune mechanism is not detectable. The majority of these reactions imitate the clinical features of milder immediate reactions (erythema, urticaria), but greater severity, even a lethal outcome are possible.

There is no difference between the clinical manifestations of immune-mediated and non-immune-mediated reactions. They both may involve the cutaneous, respiratory, gastrointestinal, or cardiovascular systems. The management of both types of reactions is the same; in addition, in the literature the two terms are often used interchangeably to describe infusion-related reactions.

The key elotuzumab related events have been infusion related AEs in all studies. Infusion reactions have been mitigated with premedications consisting of corticosteroids, H1 and H2 antagonists, and acetaminophen. Prior to the initiation of an adequate premedication regimen in the phase 1 trial, infusion reactions were observed in 52-89% of subjects.

The most frequent elotuzumab peri-infusional AEs that occurred in ≥ 10% of subjects across all Phase 1 studies, regardless of causality, include nausea, vomiting, chills, infusion-related reaction, flushing, dyspnea, cough, headache, dizziness, and rash.

1.4.2 Carfilzomib

Carfilzomib is a second-generation selective and irreversible proteasome inhibitor, which as a single agent has demonstrated clinical activity in patients with relapsed/refractory multiple myeloma. The proteasome is an intracellular protease complex that is responsible for the ubiquitin-dependent turnover of cellular proteins in normal and malignant cells. An important role of the proteasome in the context of multiple myeloma is the regulation of nuclear factor NF-κB. The chymotrypsin-like domain of the proteasome has been shown to be

the rate-limiting step of proteolysis in vitro and in vivo Bortezomib was the first proteasome inhibitor to be introduced in myeloma treatment and has gained a central role in treatment of several treatment lines in the era of novel drugs However, it has a high incidence of peripheral neuropathy causing cessation of treatment in a proportion of patients, and resistance development along the time is a rule. The side effect profile of carfilzomib is milder than with bortezomib, and especially the incidence of neuropathy is significantly lower. The most common side effects are cytopenias, in particular thrombocytopenia and anemia, fatigue, nausea, dyspnea, diarrhea and pyrexia. (incidence ≥ 30%). However, most of these side effects were mild and only the cytopenias were of grade 3 or 4 in more than 10% of the patients. Some severe side-effects have rarely been observed in phase 2 trials. Thus, cardiac failure events (e.g., cardiac failure congestive, pulmonary edema, ejection fraction decreased) were reported in 7% of patients. Pulmonary arterial hypertension was reported in 2% of patients. Tumor lysis syndrome occurred following carfilzomib administration in < 1% of patients (For FDA approved highlights of prescribing information:
http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202714lbl.pdf).

Overall, the safety profile of carfilzomib is favorable, especially a low incidence of peripheral neuropathy. In addition, data from a recent study indicate that carfilzomib can be safely administered in patients with renal failure. Palumbo et al. treated in a phase II trial 34 elderly (≥ 65 years) patients with newly diagnosed myeloma with CAR-CY-DEX (https://ash.confex.com/ash/2012/ webprogram/Paper46801.html). This drug combination had encouraging anti-myeloma activity and the side effects were acceptable. Four patients (21%) required carfilzomib dose reductions due to adverse events (grade III and IV) and no patient discontinued treatment.

Carfilzomib monotherapy has demonstrated clinical activity in patients with relapsed/refractory multiple myeloma. The PX-171-003-A1 study included multiple myeloma patients with a median of 5 previous lines of treatment and 83% of the patients had progressed on or within 60 days of last therapy. In this

cohort of heavily pretreated patients the overall response rate was 24% on single agent carfilzomib with a median duration of response of 7.4 months. The results of this study formed the basis of US Food and Drug Administration (FDA) approval in 2012 of carfilzomib for myeloma patients who have received at least two prior therapies, including bortezomib and an immunomodulatory agent, and have demonstrated disease progression on or within 60 days of the completion of the last therapy.

Favorable toxicity profile of carfilzomib makes it a suitable candidate for combination regimens. Two randomized phase 3 studies have been published. In the ASPIRE study (published in January 2015 in NEJM) combination of CAR + LEN + Dex was compared with LEN + DEX in 792 patients with relapsed myeloma. CAR combination appeared to be more efficient: ORR (PR or better) figures were 87 % and 67 %, with complete responses in 32 and 9 %, respectively. The better efficacy was also seen in PFS: 26.3 vs 17.6 months, respectively. In the other phase 3 trial (ENDEAVOUR, published in January 2016 in Lancet Oncology) CAR + Dex was compared with bortezomib + Dex in relapsed or refractory myeloma. Again, combination of carfilzomib was more efficient: objective responses were observed in 77 % vs 63 %, and complete responses in 13 % vs 6 %, respectively. Moreover, median PFS was 18.7 vs 11.1 months ($p<0.0001$), respectively. The toxicity profile in these two studies was favorable: CAR did not significantly add any toxicity in comparison to the comparative arm with the exception of hypertension which occurred more commonly in the CAR arm in both studies. Peripheral neuropathy was rarely found in the CAR arm.

Regarding the optimal dosing, data from phase 2 studies indicates superiority of the carfilzomib dose at 27 mg/m^2 compared to patients receiving 20 mg/m^2 (28). This analysis indicates a 4.1-fold higher probability of achieving partial remission or better on the 27 mg/m^2 dose compared to a dose of 20 mg/m^2. In the ASPIRE study, the dose of 27 mg/m^2 whereas in the ENDEAVOUR study with only

dexamethasone combination, a dose of 56 mg/m^2 was used with acceptable toxicity.

1.4.2.1 Carfilzomib 70 mg/m^2 weekly dosing in this study

There are four phase 3 studies in multiple myeloma, three for relapsed/refractory patients: ASPIRE (NCT01080391,PX-171-009), FOCUS (NCT01302392, PX-171-011), ENDEAVOR (NCT01568866, 2011-003) and one for newly diagnosed patients; CLARION (NCT01818752, 2012-005), all of these with twice weekly dosing. Phase 1b/2 study CHAMPION-1 is for relapsed or refractory patients to investigate higher doses of carfilzomib given once-weekly.

The PX-171-007 phase 1b/2 study was the first to evaluate the maximum tolerated dose of twice-weekly single carfilzomib dosing for RRMM patients (Papadopoulos 2014). Carfilzomib was given as monotherapy on days 1, 2, 8, 9, 15 and 16 in a 28-day cycle. Cycle 1 day 1 -2 doses were 20 mg/m^2 followed by dose escalation to 36, 45, 56 or 70 mg/m^2. Carfilzomib was administered later with low-dose dexamethasone 40 mg weekly at the 45 and 56 mg/m^2 dose levels. Dose limiting toxicities (DLT) were found in 2/33 subjects at dose 70 mg/m^2, grade 3 renal tubular necrosis and proteinuria. The MTD was therefore determined to be 56 mg/m^2. The most common AEs in this dose cohort were nausea, dyspnea, fatigue, pyrexia, thrombocytopenia and chills with a majority of grade 1-2. Overall response rate (ORR) with carfilzomib monotherapy 20/27 mg/m^2 in earlier phase 2 PX-171-003 study, were majority of patients were IMiDs and bortezomib refractory, was 23.7% patients, when ORR with this 56 mg/m^2 dose was 50% in similar population. Based on this PX-171-007 study higher doses of carfilzomib on a twice-weekly schedule given over 30 minutes were well tolerated and effective with an acceptable safety profile and this has led to the study CHAMPION 1 where higher once weekly dosing of carfilzomib will be investigated.

In CHAMPION 1, phase 1b/2 study for relapsed MM patients with 1-3 prior therapies, the dose-escalation part (n=27) included the dose of 20 mg/m^2 on day 1 cycle 1 followed by test doses on days 8 and 15 of cycle 1 in 28-day cycles. The dose escalation was from 45 mg/m^2 to 56, 70 and 88 mg/m^2 on days 1, 8, 15 combined with dexamethasone 40 mg on days 1, 8, 15, 22 in cycles 1-8 and 1, 8, 15 from cycle 9 onwards. No DLTs were noticed at the dose levels of 45 -70 mg/m^2, but 88 mg/m^2 produced two DLTs; grade 3 dyspnea and vomiting. In expansion cohort of none patients one additional grade 3 dyspnea was noticed. The MTD of once-weekly carfilzomib combined with dexamethasone was determined to be 70 mg/m^2. This CHAMPION 1 phase 2 study (n=89) is ongoing, so far ORR has been 77%, ≥ VGPR 47% and for bortezomib refractory patients (52%) ORR has been 63%. Anemia and thrombocytopenia (32% altogether) have been the most common hematological AEs; and nausea and diarrhea (35%) nonhematological AEs. Grade 3 AEs in > 5% are acute renal failure (5%), fatigue (5%). Thirty-four SAEs have been reported in 19 patients (23%). Grade 4 SAEs were thrombocytopenia, atrial fibrillation, influenza pneumonia, respiratory failure, septic shock and aphasia in four patients, and three grade 5 SAEs were reported in three patients; acute renal failure, cardio-respiratory arrest and disease progression. The preliminary results of CHAMPION 1 study have showed acceptable safety and tolerability profile and promising efficacy for once-weekly carfilzomib 70 mg/m^2 (30 minute infusion) combined with dexamethasone 40 mg weekly for relapsed and refractory MM patients and this has led to the ARROW phase 3 study where once-weekly carfilzomib 70 mg/m^2 is compared to 20/27 mg/m^2 twice-weekly dosing with superiority design.

Clinical pharmacodynamics and pharmacokinetics of carfilzomib

Proteasome inhibition with carfilzomib is irreversible due to covalent bonds between the drug and the chymotrypsin-like protease site. Therefore the drug activity is less influenced by its rapid clearance than by the rate of new

proteasome generation (Muchter et al. Eur J Haemat 2016). Pharmacodynamic data showed that the proteasome inhibition level was higher one hour after carfilzomib 70 mg/m^2 dose compared to 27 and 56 mg/m^2 doses.
Once-weekly 70 mg/m^2 carfilzomib 30-minute infusion had a mean terminal half-life comparable with the half-life of ≤ one hour of twice-weekly dosing 20/27 mg/m^2 in 2-10 minutes. The area under the curve (AUC) after 70 mg/m^2 was 1045 ng•h/ml, which is higher than the total weekly AUC after the twice-weekly of 27 mg/m^2, 758 ng•h/ml. The mean C_{max} after 30-minute infusion of 70 mg/m^2 is lower than the mean C_{max} after 27 mg/m^2 in 2-10 minutes, 2640 ng/ml and 4232 ng/ml, respectively. Drug clearance is by peptidase cleavage and epoxide hydrolysis into non-active metabolite rather than direct renal excretion or liver metabolism (Muchter et al.). Higher AUC was associated with improved responses and ORR. Both PD and PK results support the once-weekly 70 mg/m^2 administration to be investigated in MM studies.

Renal impairment

Carfilzomib is preferentially enzymatically metabolized than renally excreted. Similar duration of carfilzomib exposure and clearance and similar toxicity have been observed regardless of renal function. Therefore carfilzomib is considered safe with any level of renal function (Muchter et al.). This study does not include patients on dialysis.

Hepatic impairment

The metabolism of carfilzomib is mainly non-hepatic and its inactive metabolites are excreted into urine and bile. Drug interactions are unlikely because cytochrome P450 has no significant effect on carfilzomib metabolism. Carfilzomib has not been investigated in patients with hepatic impairment, therefore its safety in hepatic failure is unknown.

1.4.2.2 CARFILZOMIB-RELATED ADVERSE EVENTS

CLINICAL SAFETY AND DRUG-RELATED ADVERSE EVENTS

TABLE 5. Reported side effects for carfilzomib.

Body System	Very Common (may affect more than 1 in 10 people)	Common (may affect up to 1 in 10 people)	Uncommon (may affect up to 1 in 100 people)	Rare (may affect up to 1 in 1000 people)
Blood	Low red blood cell count, which may cause tiredness and fatigue; Low platelets, which may cause easy bruising or bleeding; Low white blood cell count, which may decrease your ability to fight infection;	Low white blood cell count, which may be associated with fever;		Thrombotic Thrombocytopenic Purpura/Hemolytic Uremic Syndrome (TTP/HUS) (see 'Conditions you need to look out for') Thrombotic microangiopathy (see 'Conditions you need to look out for')
Heart		Heart failure, and heart problems including rapid, strong or irregular heartbeat	Heart attack; Reduced blood flow to the heart	
Lung	Shortness of breath; Cough	Blood clot in the lungs; Fluid in the lungs; Nose bleed; Change in voice or hoarseness; Pain in throat; Wheezing; Pulmonary hypertension (see 'Conditions you need to look out for')	Lung problems (see 'Conditions you need to look out for')	
Eye		Blurred vision, Cataract		

Body System	Very Common (may affect more than 1 in 10 people)	Common (may affect up to 1 in 10 people)	Uncommon (may affect up to 1 in 100 people)	Rare (may affect up to 1 in 1000 people)
Intestinal	Diarrhea; Nausea; Constipation; Vomiting; Stomach Pain	Indigestion; Toothache		
General	Tiredness (fatigue); Fever; Swelling of the hands, feet or ankles; General weakness; Infusion reactions (see 'Conditions you need to look out for')	Pain; Chills; Feeling too hot; Pain, swelling, irritation or discomfort where you received the injection into your vein	Multi-organ failure;	
Liver		Liver problems including an increase in your liver enzyme in the blood	Liver failure; Itchy skin, yellow skin, very dark urine and very pale stools which may be caused by a blockage in the flow of bile from the liver (cholestasis)	
Infections	Respiratory tract infection; Lung infection (pneumonia); Runny nose or nasal congestion	Sore throat; Bronchitis; Urinary tract infection; Inflammation of the nose and throat; Flu-like symptoms (influenza); Serious infection in the blood (sepsis); Viral infection		
Metabolism	Decreased appetite	Dehydration	Tumor lysis syndrome (TLS) (see "Conditions you need to look out	

Body System	Very Common (may affect more than 1 in 10 people)	Common (may affect up to 1 in 10 people)	Uncommon (may affect up to 1 in 100 people)	Rare (may affect up to 1 in 1000 people)
			for')	
Bone and Muscle	Back pain; Joint pain; Pain in limbs, hands or feet; Muscle spasms	Bone and muscle pain; Chest pain; Muscle weakness; Aching muscles		
Nervous System	Headache; Dizziness; Numbness. tingling; or decreased sensation in hands and/or feet			Posterior reversible encephalopathy syndrome (PRES) (see 'Conditions you need to look out for')
Psychiatric	Insomnia (difficulty sleeping),	Anxiety		
Kidney		Kidney problems, including decreased ability to make urine, increased creatinine in the blood, and kidney failure needing dialysis		
Skin		Rash; Itchy skin; Redness of the skin; Increased sweating		
Tests	Changes to blood tests (decreased blood levels of potassium, increased blood levels of sugar and/or creatinine)	Changes to blood tests (decreased blood levels of sodium, magnesium, protein, calcium or phosphate, increased blood levels of calcium, uric acid, potassium, bilirubin, or c-reactive protein)		
Immune System			Allergy to carfilzomib	

Body System	Very Common (may affect more than 1 in 10 people)	Common (may affect up to 1 in 10 people)	Uncommon (may affect up to 1 in 100 people)	Rare (may affect up to 1 in 1000 people)
Blood vessels	High blood pressure (hypertension)	Low blood pressure (hypotension); Blood clots in the veins	Stroke; Extremely high blood pressure (see 'Conditions you need to look out for')	

Important new safety information: In June, Amgen/Onyx has released new safety information on Carfilzomib based on the recently completed phase 3 trial. The information regards three types of adverse events:
Hypertension including hypertensive crises: Hypertensive crises have been reported in <1% of patients. The recommendation is that patients are routinely evaluated for hypertension.
Pulmonary hypertension: Pulmonary hypertension has been reported in approximately 1% of patients. The recommendation is to evaluate pulmonary symptoms, stop carfilzomib until resolved or returned to baseline, and consider whether to restart carfilzomib.
Pulmonary toxicities: Interstitial lung disease (including pneumonitis), acute respiratory failure and ARDS have been reported in <1% of patients. The recommendation is to evaluate pulmonary symptoms, stop carfilzomib until resolved or returned to baseline, and consider whether to restart carfilzomib.

1.4.3 Dexamethasone

Allergic Reactions: Anaphylactoid reaction, anaphylaxis, angioedema.

Cardiovascular: Bradycardia, cardiac arrest, cardiac arrhythmias, cardiac enlargement, circulatory collapse, congestive heart failure, fat embolism, hypertension, hypertrophic cardiomyopathy in premature infants, myocardial rupture following recent myocardial infarction, edema, pulmonary edema, syncope, tachycardia, thromboembolism, thrombophlebitis, vasculitis.

Dermatologic: Acne, allergic dermatitis, dry scaly skin, ecchymoses and petechiae, erythema, impaired wound healing, increased sweating, rash, striae, suppression of reactions to skin tests, thin fragile skin, thinning scalp hair, urticaria.

Endocrine: Decreased carbohydrate and glucose tolerance, development of cushingoid state, hyperglycemia, glycosuria, hirsutism, hypertrichosis, increased requirements for insulin or oral hypoglycemic agents in diabetes, manifestations of latent diabetes mellitus, menstrual irregularities, secondary adrenocortical and

pituitary unresponsiveness (particularly in times of stress, as in trauma, surgery, or illness), suppression of growth in pediatric patients.

Fluid and Electrolyte Disturbances: Congestive heart failure in susceptible patients, fluid retention, hypokalemic alkalosis, potassium loss, sodium retention.

Gastrointestinal: Abdominal distention, elevation in serum liver enzyme levels (usually reversible upon discontinuation), hepatomegaly, increased appetite, nausea, pancreatitis, peptic ulcer with possible perforation and hemorrhage, perforation of the small and large bowel (particularly in patients with inflammatory bowel disease), ulcerative esophagitis.

Metabolic: Negative nitrogen balance due to protein catabolism.

Musculoskeletal: Aseptic necrosis of femoral and humeral heads, loss of muscle mass, muscle weakness, osteoporosis, pathologic fracture of long bones, steroid myopathy, tendon rupture, vertebral compression fractures.

Neurological/Psychiatric: Convulsions, depression, emotional instability, euphoria, headache, increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment, insomnia, mood swings, neuritis, neuropathy, paresthesia, personality changes, psychic disorders, vertigo.

Ophthalmic: Exophthalmos, glaucoma, increased intraocular pressure, posterior subcapsular cataracts.

Other: Abnormal fat deposits, decreased resistance to infection, hiccups, increased or decreased motility and number of spermatozoa, malaise, moon face, weight gain.

Dexamethasone: It may not be excluded that the efficacy of oral contraceptives may be reduced during dexamethasone treatment. Effective measures to avoid pregnancy must be taken.

1.5 OVERALL RISK/BENEFIT ASSESSMENT

Elotuzumab has been evaluated in several studies for RRMM patients and studies for newly diagnosed MM patients are ongoing. It has proved to have acceptable safety and efficacy combined with both lenalidomide and bortezomib. It has not

previously investigated with carfilzomib and in this study design carfilzomib has weekly dosing instead of approved twice-weekly dosing. Therefore first 5 patients will have reduced weekly dose of carfilzomib, 56 mg/m^2, and side effects and tolerability will be followed carefully, and is safety the following patients will have carfilzomib 70 mg/m^2 weekly dosing. This weekly dosing is challenging the accepted twice-weekly dosing in ARROW-study with superiority design, so the efficacy will be most probably beneficial.

1.6 RESEARCH HYPOTHESIS

2nd generation PI, carfilzomib, has proved to be more efficient than the 1st generation PI bortezomib with reduced number of peripheral neuropathy side effects. Elotuzumab is a monoclonal antibody directing SLAMF7 (CS-1), which is highly expressed on myeloma cells and also on natural killer cells. Immuno-hematological approach is the most interesting research field at this moment, and we have designed this phase 2 study to investigate the combination of carfilzomib and elotuzumab plus dexamethasone in multiple myeloma patients after 1 – 3 prior treatment lines. The hypothesis is that this new combination will be more effective than alternative therapies outside trial available at this moment for relapsed/progressed MM patients who have had mostly bortezomib- and lenalidomide-based treatments,

1.7 STUDY RATIONALE

Multiple myeloma is regarded as an incurable disease. The vast majority of patients have recurrent relapses in the course of disease proceeding into end-stage RRMM phase, extramedullary disease or secondary plasma cell leukemia. Even with the introduction of IMiDs and PIs the 5-year overall survival is still only 66% (Bergsagel ASCO). With the next generation PIs and monoclonal antibodies the treatment responses of RRMM have improved. ASPIRE study showed that 3-drug combination in RRMM patients of carfilzomib, lenalidomide and dexamethasone is superior to lenalidomide and dexamethasone in terms of ORR,

CR and PFS and the PFS of 26 months is more than before observed in this setting. ELOQUENT-2 study demonstrated the efficacy and synergy of 3-drug combination lenalidomide, elotuzumab and dexamethasone compared to lenalidomide plus dexamethasone and ENDEAVOR study showed carfilzomib plus dexamethasone to be more effective than 1st generation PI bortezomib combined with dexamethasone. The possible combination efficacy and synergy of proteasome inhibitor with elotuzumab has now investigated in elotuzumab (E), bortezomib (B) and dexamethasone (d) study, which showed PFS of 9.7 months for E-Bd compared to 6.9 months for Bd arm. Patients in E-Bd arm had 24% reduction of risk of PD or death (Palumbo et al.). This gives rationale for this phase 2 study, where the feasibility of 2nd generation carfilzomib and elotuzumab plus dexamethasone will be investigated.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Primary objective

To investigate the safety and feasibility of carfilzomib + elotuzumab + dexamethasone combination and initial efficacy with relapsed or progressed multiple myeloma patients

2.1 Primary endpoint

- The primary endpoint of this study is overall response rate.

2.2 Secondary endpoints

- Complete remission
- Safety
- Minimal residual disease assessment (measured if at least VGPR response)
- Duration of response
- Time to next treatment

- Progression-free survival

3. ETHICAL AND REGULATORY CONSIDERATIONS

The study will be conducted in accordance with the ethical principles of the Declaration of Helsinki, the ICH-GCP Guidelines, the EU Clinical Trial Directive (2001/20/EG), as may be amended or replaced, and applicable regulatory requirements. The local investigator is responsible for the proper conduct of the study at the study site. Approval of the study protocol and any substantial amendment will be requested from the National Ethics Committees of Finland and Sweden, the Finnish Medicines Agency and the Swedish Health Authority Medical Products Agency (MPA) by the Sponsor-Investigator. The Sponsor-Investigator will provide National Ethics Committees` and the Finnish Medicines Agency's and Medical Products Agency`s above mentioned approvals to Bristol-Myers Squibb and Amgen.

In accordance with the Declaration of Helsinki patients have the right to withdraw from the protocol at any time for any reason. The investigator also has the right to withdraw patients from the protocol in the event of intercurrent illness, adverse events and treatment failure after a prescribed procedure, protocol violations, cure, administrative reasons or other reasons. If a patient decides to withdraw from the protocol, all efforts will be made to complete and report the observations as thoroughly as possible. A complete final evaluation at the time of the patient's withdrawal should be made together with the reason.

The clinical trial investigator-sponsor is the physical person or legal entity which is interested in the performance of the trial, signs requests for authorization addressed to the National Ethics Committee (EC) and regulatory authority of Finland and is responsible for the trial, including its performance, initiation and completion. The investigator-sponsor will be responsible for ensuring compliance with applicable legal guidelines. Investigators must agree with this protocol and

know in detail the properties of the drug used in this clinical trial. Investigators must provide the patient with a patient information sheet and help him/her to understand the explanation provided. It is important to tell the patient that his/her participation in the study is completely voluntary and that it will not affect patient-physician relationship. In addition, it will be guaranteed that all people involved in the study will observe the confidentiality of any information related to the patient. All participants in the study are covered by the National Pharmaceutical Insurance Pool.

Each patient is assigned a unique patient study number at registration. In study documents the patient´s identity is coded by patient study number. The local investigator will keep a subject enrolment and identification log that contains the key to the code, the personal identification data linked to each patient study number. This data is filed at the investigational site and should only be accessed by the investigator and the supporting site staff or by representatives of the sponsor-investigator or a regulatory agency for the purpose of monitoring visits or audits and inspections. The Information and Consent Form also explains that for data verification purposes an authorized regulatory authority, or an ethics review board may require direct access to parts of the hospital or practice records relevant to the study including patients' medical history.

Quality of Life questionnaire and data analysis

Nordic Myeloma Study Group has developed collaboration with Quality of Life Center of Odense University Hospital in Denmark. The same paper form used already in this trial will be changed to computer-based questionnaire. Patients will fill the electronic questionnaire and the data will be sent electronically to Odense for analysis including the study code of the patient. Data cannot be totally anonymous because the results will be compared with the treatment response.

3.1 INFORMED CONSENT

Written informed consent of patient is required before any study related procedure. The investigator should provide enough time for patient to discuss about all details of the study. All questions concerning the study will be answered to the satisfaction of the patient before possible obtaining of consent. The content of the patient information letter, informed consent form and any other written information provided to patients will be in compliance with ICH-GCP and other applicable regulations and should be approved by the Ethics Committee before use. Whenever new important information, relevant to the patients´s consent, will be available, the patient information letter, informed consent and any other written information will be revised. Any revised informed consent form and written information should be approved by the Ethics Committee before use. The patient should be informed in a timely manner if new information becomes available that might be relevant to the patients´s willingness to continue participation in the study.

3.2 PATIENT CONFIDENTIALITY

Each patient is assigned a unique patient study number at registration. In study documents the patient´s identity is coded by patient study number. In some cases date of birth is also listed. The local investigator will keep a subject enrolment and identification log that contains the key to the code, the personal identification data linked to each patient study number. This data is filed at the investigational site and should only be accessed by the investigator and the supporting site staff or by representatives of the sponsor-investigator or a regulatory agency for the purpose of monitoring visits or audits and inspections. The Information and Consent Form also explains that for data verification purposes an authorized regulatory authority, or an ethics review board may require direct access to parts

of the hospital or practice records relevant to the study including patients' medical history.

3.3. STUDY INSURANCE

Before the start of the study the sponsor-investigator and principal investigator of each site will ensure that adequate insurance for patients is in place covering losses due to death or injury resulting from the study, in accordance with applicable laws and regulations in each country where the trial is conducted (Finland, Sweden). Adequate insurance for investigators and study staff will be ensured. The pharmaceutical company supplying drugs used in the study must have their own liability insurance.

4. INVESTIGATIONAL PLAN Study design and duration

This is an investigator initiated, academic, non-randomized, open-label multicenter phase 2 study for patients with multiple myeloma in relapse or progression after 1 to 3 prior treatment lines and in need of therapy.

All patients will receive successive cycles of CAR + ELO + Dex according to the schedule shown in Table 2 and 6. Cycles are to be continued until progression, relapse or excess toxicity. The primary objective is to assess the overall response rate obtained with the regimen. This study will have phase 2a portion with 40 included patients to show the feasibility and safety of this design and if observed will be expanded to phase 2b portion with additional number of patients based on statistical power calculations..

4.1 Study procedures:

At registration each patient will have an unique identification number and following details will be documented:

- Name of study center and responsible investigator
- Date of birth of study patient
- Date of signed informed consent

- Date of treatment start

The study patient is considered enrolled on first day of study protocol treatment. Any study related investigations are not started before written informed consent.

- At inclusion: before the start of protocol treatment blood- and urine values within 2 weeks before study start, bone marrow samples within 4 weeks and bone imaging within 2 months
- During treatment: within 5 days before next cycle
- At progression and if patient is taken/withdrawn off protocol

All patients will be followed until 3 years after onset of the treatment protocol.

4.2 STUDY POPULATION

4.2.1 Inclusion criteria

Each patient must meet all of the following inclusion criteria to be enrolled in the study:

1. Male or female patients at the age of 18 to below 75 years with the life expectancy of at least three months.

2. Prior confirmed diagnosis of multiple myeloma and measurable disease in blood or urine with at least one of the following: Serum M-protein ≥ 5g/l, Urine M-protein ≥ 200 mg/24 hours, In subjects without detectable serum or urine M-component, serum free light chain (S-FLC) > 100 ml/l (involved light chain) and an abnormal serum kappa/lambda ratio

3. Relapse or progression after 1 to 3 prior treatment lines, which have included proteasome inhibitors (bortezomib, carfilzomib and/or ixazomib) and/or lenalidomide. Refractoriness to bortezomib, ixazomib and/or lenalidomide is allowed in the preceding cycle. Patients with previous autologous transplantation can be included.

4. Need of treatment of relapse or progression: IMWG criteria for relapse/progression (paraprotein or CRAB criteria or both). (Appendix 5)

5. Voluntary written consent must be given before performance of any study related procedure not part of standard medical care, with the

understanding that the patient may withdraw consent at any time without prejudice to future medical care.

6. Females of childbearing potential (FCBP) must have a confirmed negative serum pregnancy test within the 7 days prior to inclusion
7. Females of childbearing potential must use one effective method of contraception and their partners condom during the study and for 120 days following the last study drug treatment dose and male subjects who are sexually active with FCBP must agree to use condom during the study and for 180 days following the last study drug treatment dose.
8. Eastern Cooperative Oncology Group (ECOG) performance status 0-2, or Karnofsky at least 60. (Appendix 1)
9. Patients must meet the following adequate organ and bone marrow function within 21 days prior to inclusion:

    - Absolute neutrophil count (ANC) 1,000/mm^3 ($\geq$ 1.0 x 10^9/L) and platelet count 75 x 10^9/L. Platelet transfusions to help patients meet eligibility criteria are not allowed within 3 days before study enrollment. Granulocyte growth factors are allowed to meet the inclusion criteria.

    - Hemoglobin (Hb) $\geq$ 80 g/l (use of erythropoietin and red blood cell transfusions allowed by institutional guidelines, however the most recent RBC may not have given within 7 days prior to obtaining screening Hb

    - Total bilirubin < 1.5 times the upper limit of the normal range (ULN).

    - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) < 3 times the ULN.

    - Calculated creatinine clearance $\geq$ 40 mL/min (Cockcroft-Gault estimation of creatinine clearance (CRcl): CRcl (mL/min) = (140 - age) x (weight [kg]) / 72 x (serum creatinine [mg/dL]); for females, multiply by 0.85 (Cockcroft DW. 1976, Luke DR. 1990)(Appendix 2).

10. Patient must be willing and able to adhere to the study protocol visit schedule and other protocol requirements.

11. Negative pregnancy test at inclusion if applicable

4.2.2. Exclusion criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study:

1. Female patients who are lactating or have a positive serum pregnancy test during the screening period.

2. Major surgery within 28 days before enrollment.

3. Radiotherapy within 14 days before enrollment, but if the involved field is small, 7 days will be considered a sufficient interval before onset of the treatment.

4. Glucocorticoid therapy within the 14 days prior to inclusion that exceeds a cumulative dose of 160 mg dexamethasone or 1000 mg prednisone.

5. Central nervous system involvement.

6. Infection requiring systemic antibiotic therapy or other serious infection within 14 days before study enrollment.

7. Active congestive heart failure (NYHA III-IV) (Appendix 3), symptomatic ischemia, conduction abnormalities uncontrolled by conventional intervention, acute diffuse infiltrative pulmonary disease, pericardial disease or myocardial infarction within 6 months prior to enrollment or left ventricular ejection fraction (LVEF) <40% within one month before randomization.

8. Ongoing or active systemic infection, active hepatitis A, B or C virus infection, or known human immunodeficiency virus (HIV) positivity.

9. Any other serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.

10. Known allergy to Captisol (a cyclodextrin derivative used to solubilize carfilzomib) or to any of the study medications, their analogues, or excipients in the various formulations of any agent.

11. Contraindication to dexamethasone or any of the required concomitant drugs or supportive treatments, including hypersensitivity to antiviral drugs, or intolerance to hydration due to pre-existing pulmonary or cardiac impairment.

12. Diagnosed or treated for another malignancy within 5 years before study enrollment or previously diagnosed with another malignancy and have any evidence of residual disease. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.

13. Patient has ≥ Grade 3 peripheral neuropathy, or Grade 2 with pain on clinical examination within the 14 days prior to inclusion.

14. Participation in another interventional study within the 28 days before this study inclusion.

15. Patients refractory to carfilzomib or elotuzumab.

16. Primary plasma cell leukemia, systemic AL amyloidosis, Waldenström macroglobulinemia, rare IgM multiple myeloma, POEMS syndrome, myelodysplasia

17. Allogeneic or autologous stem cell transplantation planned

18. Participants receiving any other investigational agents or received within 60 days

19. Pleural effusions requiring thoracocentesis within the 14 days prior the inclusion.

20. Ascites requiring ascitespunction within the 14 days prior to inclusion.

21. Previous allogeneic transplantation

22. Uncontrolled hypertension or uncontrolled diabetes despite medication

23. Known hepatic cirrhosis

24. Severe autoimmune disease

25. Positive direct antiglobulin test (DAT), Coombs test

4.2.3 DISCONTINUATION OF SUBJECTS FROM TREATMENT

Patients will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. The investigator has also the right to withdraw patient from the study for any of the following reason.

Adverse event

Protocol violation

Lost to follow-up

Progressive treatment

Study termination

If the responsible physician thinks a change of therapy would be best for the patient

No compliance of the patient

Pregnancy

Death

Patients who are withdrawn will not be replaced. At the time of withdrawal, all study procedures outlines for the end of visit should be completed (Table 1. End of study). The primary reason for patient´s withdrawal from the study is recorded in the source documents and CRF. If withdraw by investigator or patient will occur, the patient undergoes an end of study assessment, in which present disease stage and reason for end of study should be noted and be given appropriate care under medical supervision until symptoms cease or the condition becomes stable.

4.2.4 DISCONTINUATION IN CASE OF INTOLERABILITY

Patients will continue study treatment with dose reduction by the protocol in case of intolerability by the investigator decision. Study patient can continue study treatment with 1-2 drug combination if one of the study drugs has to be permanently discontinued.

5. TREATMENT

5.1 TABLE 6. STUDY DRUG ADMINISTRATION SCHEDULE

28-day cycle, carfilzomib will be infused first

Cycles 1-2			
Agent	**Dose/day**	**Route**	**Days**
Carfilzomib patients 1-5 patients 1-5	 20 mg/m^2 56 mg/m^2 56 mg/m^2	 IV IV IV	 1 (cycle 1) 8, 15 (cycle 1) 1, 8, 15 (cycle 2)
Elotuzumab	10 mg/kg	IV	1, 8, 15
Dexamethasone	40 mg	Oral/IV	1, 8, 15, 22

Cycles 1-2			
Agent	**Dose/day**	**Route**	**Days**
Carfilzomib -patients 6-40	 20 mg/m^2 70 mg/m^2 70 mg/m^2	 IV IV IV	 1 (cycle 1) 8, 15 (cycle 1) 1, 8, 15 (cycle 2)
Elotuzumab	10 mg/kg	IV	1, 8, 15
Dexamethasone	40 mg	Oral/IV	1, 8, 15, 22

Cycles 3-8			
Agent	**Dose/day**	**Route**	**Days**
Carfilzomib - patients 1-40	70 mg/m^2	IV	1, 8, 15
Elotuzumab	10 mg/kg	IV	1,15
Dexamethasone	40 mg	Oral/IV	1, 8, 15, 22

Cycles 9 – until relapse or progression			
Agent	**Dose/day**	**Route**	**Days**
Carfilzomib - patients 1-40	70 mg/m^2	IV	1, 15
Elotuzumab	10 mg/kg	IV	1,15
Dexamethasone	40 mg	Oral/IV	1,15

5.2 CARFILZOMIB ADMINISTRATION

Patients will receive iv prehydration prior to each carfilzomib infusion during cycle 1. Prehydration will consist of 250 to 500 ml normal saline or other appropriate iv fluid.

Thereafter, carfilzomib prehydration should only be administered if the patients condition and/or risk factors require hydration. The total amount of prehydration will be reported and the reason for hydration after cycle 1 will be reported. Carfilzomib will be administered as an iv infusion over 30 minutes.

Carfilzomib for injection is supplied as a lyophilized parenteral product in single-use vials packaged in multi-vial cartons. Institutional pharmacies will be supplied with vials with adequate study labeling. Study treatments should be stored in a securely locked area with access limited to appropriate study personnel. Carfilzomib must be stored at 2°C to 8°C in a refrigerator. Carfilzomib vials must be kept in cartons in order to protect from light until ready for reconstitution. One carfilzomib is reconstituted and inspected, the clear solution may be stored in a refrigerator (recommended) controlled temperature from 2°C to 8°C for up to 24 hours. Once reconstituted, carfilzomib must be used within 4 hours if not refrigerated and within 24 hours if it has been stored in a light-tight refrigerator. The lyophilized product is reconstituted with sterile water for injection, to a final carfilzomib concentration of 2.0 mg/ml prior to administration. The dose will be calculated using the patient´s actual body surface area (BSA) at baseline. Patients with a BSA > 2.2 m^2 will receive a dose based upon a 2.2 m^2 BSA. Dose adjustments must be made for weight gains/losses of ≥ 20% of baseline body weight.

Mechanical infusion pumps are recommended but gravity-dependent infusions are permitted if the 30-minute infusion duration can be reliable maintained.

Carfilzomib infusion must occur at a facility capable of managing hypersensitivity reactions. Patients will be hospitalized overnight after first infusion of the study drug combination. Patients will remain at the investigational site under observation for at least one hour following each infusion of carfilzomib in cycle 1. Carfilzomib must be administered via a dedicated iv line. If a permanent infusion device (e.g. Porta-Cath) is used for infusion the line must be flushed with a minimum of 20 ml of normal saline prior to and following carfilzomib infusion.

5.2.1 DOSE MODIFICATION GUIDELINES FOR CARFILZOMIB

In a case of study related adverse event the clinical investigator must assess its possible relationship to carfilzomib in addition to elotuzumab and dexamethasone.

Table 7. Carfilzomib dose reduction guidelines for toxicity and dose modification

	1st dose reduction	2nd dose reduction	3rd dose reduction
70 mg/m^2	56 mg/m^2	45 mg/m^2	36 mg/m^2

The basic principle is that if a patient requires an interruption of carfilzomib of more than four weeks this study patient will be removed from study; all exceptions to this must be discussed with principal investigator. If the carfilzomib dose is reduced once, it will be continued for at least one cycle. In case of excellent toleration of this cycle, the dose level prior to reduction may be resumed by the investigator´s discretion.

Table 8.
Carfilzomib dosing guidelines for treatment- emergent hematologic toxicity

Hematologic toxicity	Recommended action
Thrombocytopenia	
If platelets ≤ 30 x 10^9/l	If 10-30 x 10^9/l without bleeding continue the same dose If evidence of bleeding or platelets < 10 x 10^9/l, withhold dose until platelets return to ≥ 10 x 10^9/l and/or bleeding is controlled, then resume the same dose
For each subsequent drop to ≤ 30 x 10^9/l	If 10-30 x 10^9/l without bleeding continue at the same dose If evidence of bleeding or platelets < 10 x 10^9/l, withhold dose until platelets return to ≥ 10 x 10^9/l and/or bleeding is controlled, then resume at 1 dose reduction.
Neutropenia	
If ANC ≤ 0.75 x 10^9/l	If ANC 0.5-0.75 x 10^9/l, continue at the same dose If ANC < 0.5 x 10^9/l, withhold dose until ANC returns to ≥ 0.5 x 10^9/l, then resume at the same dose.
For each subsequent drop to ≤ 0.75 x 10^9/l	If ANC 0.5-0.75 x 10^9/l, continue at the same dose If ANC < 0.5 x 10^9/l, withhold dose until ANC returns to ≥ 0.5 x 10^9/l, then resume at 1 dose reduction
Neutropenic fever	If ANC < 0.5 x 10^9/l, and single temperature > 38.5°C or temperature > 38.0°C more than one hour, withhold dose until ANC returns to baseline level, then resume at the same dose.

ANC = absolute neutrophil count.

Conditions not requiring dose reduction of carfilzomib

- Grade 3 nausea, vomiting or diarrhea, unless persisting more than 3 days with adequate treatment of antiemetics or antidiarrheal agents
- Grade 3 dexamethasone-related hyperglycemia
- Grade 3 fatigue, unless persisting for > 14 days
- Alopecia

Table 9. Carfilzomib dosing guidelines for nonhematologic toxicity

Nonhematogical toxicity	Recommended action
Renal dysfunction	
Serum creatinine equal to or greater than 2 x baseline, or CrCl < 15 ml/min, or decreases to ≤ 50% of baseline or need for dialysis	Withhold dose and continue monitoring the renal function If attributable to carfilzomib, resume when renal function has recovered to within 25% of baseline, start at 1 dose level reduction If not attributable to carfilzomib, dosing may be resumed at the discretion of the physician Patient will be withdrawn from study in case of permanent dialysis need
≥ grade 3 elevation in liver function tests	Withhold dose and resume at 1 dose reduction level when toxicity has recovered to baseline
Grade 3 infection	Withhold carfilzomib until infection resolves and resume at the same dose
Congestive heart disease	Any subject with symptoms of congestive heart failure, whether or not drug related, must have the dose held until return to baseline, after which treatment may continue at a reduced dose, or consider discontinuation of study protocol. If no recovery in 4 weeks, patient must be withdraw.
Left ventricular ejection fraction	
For resting LVEF < 40% or reduction of LVEF to < 55% if the drop is greater than 20% form baseline	Withhold until LVEF returns to > 40% or, if held due to a drop to < 55%, to within 15% of baseline and resume at 1 dose reduction.
Other grade 1 or 2 nonhematologic toxicity	Continue at the same dose
Any other drug-related nonhematologic toxicity ≥ grade 3	If attributable to carfilzomib, withhold dose Resume at 1 dose reduction when toxicity has resolved to grade 2 or less or to baseline If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician
PRES: posterior reversible encephalopathy syndrome; headache, altered mental status,	Stop carfilzomib and study treatment and the patient is withdrawn from study. In visual or

seizures, visual loss, hypertension	neurological symptoms neuroradiological imaging is recommended.

5.3 ELOTUZUMAB ADMINISTRATION

TABLE 10. Product information table – product description

Product description and dosage form	Potency	Primary packaging (volume)/label type	Appearance	Storage conditions (per label)
Elotuzumab powder for solution for infusion	300mg /vial or 400 mg/vial	20 ml vial /Open label	Sterile white to off-white, preservative-free, lyophilized cake	Store at 2°C −8°C Protect from light. Do not freeze or shake

Administration and handling of elotuzumab (See also Appendix 6)

The lyophilized elotuzumab drug product should be stores at 2°C to 8°C. Prior to administration the drug must be reconstituted with sterile water for injection, then further diluted in 0.9% sodium chloride normal saline. After the dose is diluted in normal saline, the elotuzumab infusion must be administered within 8 hours if stored at room temperature. If a delay is anticipated, the prepared dose may be refrigerated at 2°C to 8°C for up to 24 hours. If stored under refrigerated conditions, the prepared study drug solution should be equilibrated to room temperature (this takes 2-2.5 hours) and the container must be gently inverted to mix well before administration. Do not use the accelerated warming methods. If administration is delayed beyond the specified time, the prepared dose solution must be discarded, and the reason documented. The dose of elotuzumab to be given to a study patient will be calculated by multiplying the patient´s weight (kg) by 10 mg/kg.

Premedication before elotuzumab

Dexamethasone

On weeks without elotuzumab, administer the weekly dose of 40 mg dexamethasone orally on day 1, 8, 15, and 22 (-1 to +3 days). At the investigator's discretion, the oral dexamethasone may be given as a split dose over 2 consecutive days each week.

On weeks of elotuzumab infusion, split the weekly dose of dexamethasone between oral and IV administration as indicated below under "Premedication Before Elotuzumab"

At the discretion of the investigator, the oral dexamethasone component may be given as a split dose 12 – 24 hours and 3 hours prior to elotuzumab

Premedication before elotuzumab

1. Dexamethasone 28 mg po (between 3 - 24 hours prior to the start of elotuzumab infusion or as a split dose 12 – 24 hours and 3 hours prior to elotuzumab) and
2. Dexamethasone 12 mg IV (on the day of elotuzumab infusion 45-90 minutes prior to the start of infusion).
3. H1 blocker: diphenhydramine (25 - 50 mg po or IV) or equivalent (45-90 minutes prior to the start of infusion)
4. H2 blocker: ranitidine (50 mg IV) or equivalent (45-90 minutes prior to the start of infusion)
5. Paracetamol 500 – 1000 mg (Acetaminophen SIC! Not used in Nordic countries (650 - 1000 mg po), (45-90 minutes prior to the start of infusion)

Premedication regimen in patients with a prior infusion reaction

Subjects with prior infusion reaction must receive H1, H2 blockers and paracetamol (acetaminophen) at maximum doses specified above.

In addition, dexamethasone premedication should be administered as per the Table 11 below:

Table 11. Corticosteroid Premedication

Prior infusion reaction	Corticosteroid premedication prior to elotuzumab

Table 11. Corticosteroid Premedication

Prior infusion reaction	Corticosteroid premedication prior to elotuzumab
None or only grade 1 infusion reaction	28 mg PO dexamethasone (3 - 24 hrs prior to elotuzumab) AND 12 mg IV dexamethasone at least 45-90 min prior to elotuzumab
Prior grade 2 infusion reaction	28 mg PO dexamethasone (3 - 24 hrs prior to elotuzumab) AND 14 mg IV dexamethasone at least 45-90 min prior to elotuzumab
Prior grade 3 or recurrent grade 2 infusion reaction	8 mg oral dexamethasone (12 - 24 hrs prior to elotuzumab) AND 8 mg oral dexamethasone (at least 3 hrs prior to elotuzumab) AND 18 mg IV dexamethasone at least 45-90 min prior to elotuzumab

At the discretion of the investigator, the 28mg oral dexamethasone component may be given as a split dose: 12mg PO (12 – 24 hours prior to elotuzumab) AND 16mg PO (3 hours prior to elotuzumab).

If a subject with a prior grade 2 - 3 infusion reaction also requires dose reduction of dexamethasone, the weekly dexamethasone on the days of elotuzumab infusion should be no lower than 8 mg IV (on the day of elotuzumab infusion at least 45 minutes prior to elotuzumab).

Subjects with a grade 4 elotuzumab infusion reaction must have elotuzumab permanently discontinued.

5.4 CONCOMITANT TREATMENT

A concomitant medication is defined as any prescription or over-the-counter preparation including vitamins. For all patients all administered concomitant medications and therapies, from signing of the informed consent until 30 days after the last dose of study drug must be reported in the designated electronic case report form (eCRF). Concomitant medications required for the study and used

prophylactically will be described in the eCRF. Blood products must be reported on the appropriate eCRF.

5.4.1 REQUIRED CONCOMINANT MEDICATION

These should be initiated at least 24 hours before the first administration of carfilzomib.

Antiviral and pneumocystis jirovecii prophylaxis

Valacyclovir 500 mg po daily or an equivalent acyclovir is a required medication and should be continued for the duration of study treatment. Due to continuous dexamethasone combined with elotuzumab pneumocystis jirovecii pneumonia prophylaxis is recommended according to institutional practice.

Gastrointestinal prophylaxis

Oral proton-pump inhibitor according to institutional practice is required to prevent peptic ulcer throughout the study due to dexamethasone long-term use.

Pregnancy and contraception

Females of childbearing potential must use one effective method of contraception and their partners condom during the study and for 120 days following the last study drug treatment dose and male subjects who are sexually active with FCBP must agree to use condom during the study and for 180 days following the last study drug treatment dose. If a menstrual period in a FCBP does not occur at the anticipated time, study drug treatment must be interrupted, and a serum pregnancy test must be performed. Study drug administration may resume after documentation of negative pregnancy test.

5.4.2 OPTIONAL AND ALLOWED CONCOMITANT MEDICATIONS

Allopurinol or other approved uric acid-lowering agent is allowed to use in patients with high risk of tumor lysis syndrome due to high tumor burden. Adequate hydration must be given to reduce the risk of tumor lysis and renal impairment with these patients. Mycostatin and oral fluconazole may be used at the investigator´s decision. Antiemetics and antidiarrheal drugs are recommended

to use as necessary. Granulocyte growth factors are allowed to use in neutropenia in accordance with ASCO Guidelines, but those are not allowed to give prophylactically. Red cell and/or platelet transfusions and erythropoietin are allowed to use according to institutional guidelines if clinically needed and patients can have bisphosphonates by recommended guidelines.

5.4.3 PROHIBITED AND/OR RESTRICTED TREATMENTS

Other antimyeloma treatment than study protocol treatment during the study is not allowed. Glucocorticoids are allowed to use for nonmalignant situation like asthma with a dose of no more than ≤ 4 mg/day dexamethasone or prednisone ≤ 20 mg/day. Need of plasmapheresis indicates myeloma progression and the patient will end the study treatment.

5.5 STUDY DRUG ASSIGNING

This is open-label study without any randomization or stratification. All patients will have same study treatment protocol. The responses will be analysed additionally based on stratification by del17p, t(4;14), +1q and also by ISS stage.

5.5.1 STUDY DRUG PACKAGING AND LABELING AND ORDERING

Carfilzomib

Study drug carfilzomib will be delivered free of charge from Amgen covered with final study label on packages based on subscriptions of each study site. Study sites will fill drug medication diary during protocol treatment to document the doses.

Elotuzumab

Study drug elotuzumab will be delivered free of charge from BMS covered with final study label on packages based on subscriptions of each study site. Study sites will fill drug medication diary during protocol treatment to document the doses.

Amgen and BMS will supply study drugs free of charge for the duration of this trial and dosage will be administered by the study protocol. The drugs will be sent

as labelled for study drugs to each study site. No distribution will take place before required documentation is in place.

Dexamethasone

Dexamethasone 40 mg will be taken orally and intravenously by the specified premedication. Oral dose will be taken with the morning breakfast. This drug will be reimbursed as routine medication. Patients will fill drug medication diary during protocol treatment to document their doses.

6. STUDY ASSESSMENTS AND PROCEDURES

Study investigations will be done by the sample flowchart Table 1.

6.1. Medical previous history

- complete medical history
- symptoms of illness
- history of thrombosis of the patient and the relatives
- history of any other malignancies of the patient and relatives
- performance status (ECOG)
- infections
- bone symptoms
- bleeding
- polyneuropathy
- gastrointestinal symptoms

6.2 Physical examinations

- standard physical examination with cardiovascular and neurological (polyneuropathy, autonomic neuropathy) examinations
- orthostatic hypotension

- body weight and height, surface area
- exclusion of infections and bleedings

6.3 Hematology

- hemoglobin, hematocrit, leukocytes, leukocyte differential count, neutrophils, platelets

6.4 Blood chemistry

- creatinine, creatinine clearance (Cockcroft-Gault equation)
- liver enzymes (ALAT, AFOS, BIL)
- plasma albumin (ISS)
- serum beta-2-microglobulin (ISS, Appendix 4)
- LD
- CRP
- Ionized calcium, sodium, potassium, phosphate
- Uric acid
- E-Coombs (direct antiglobulin test, DAT) at screening and repeated if clinically unexpected anemia appears

Blood, bone marrow, and urine samples will be required at study entry and at key time-points during the treatment for biochemical, and immunophenotypic assessments, as part of scientific studies in order to monitor MRD as defined by paraprotein, serum free light chain and flow cytometry to define depth and quality of responses. In addition, cytogenetic FISH findings are utilized as prognostic and stratification markers.

6.5 Immunochemistry

Serum- and 24h urine- protein electrophoresis and immunofixation (IFE)

For measurement of M-protein at entry and to confirm CR. The samples of IgG – myeloma patients will be frozen for later analyses. Helsinki University Hospital

laboratory is developing the method for analysing the IFE samples of IgG patients who have treated with elotuzumab. Serum samples will be stored before treatment, at best response and at relapse from all patients.

Quantification of serum- or urine M-component always when response is assessed

Serum free light chain (S-FLC) assay always when response is assessed

6.6 Bone marrow assessment

Bone marrow samples at entry for multiparameter flow cytometry (MFC) (if it has not taken at diagnosis) and if VGPR/CR has been achieved and annually if response has been maintained

Bone marrow samples at entry for FISH analysis to investigate del17p and screening of translocations 4;14, 14;16 and 14;20, +1q, except the patient already has had these aberrations.

6.7 Specific additional investigations

- Bone imaging: Low-dose whole body CT, MRI, or x-ray according to local MM guidelines: at entry and if clinically indicated
- Electrocardiogram from all patients at entry and at the end of study, and if clinically indicated
- Cardiological investigations, echo at base line
- Spirometry and diffusion capacity, if clinically needed

Patients are asked to fill quality of life questionnaire at inclusion, on day 1 and 15 of cycles 1 – 8 thereafter on day 1 of each cycle and in the end of study.

7. SAFETY ASSESSMENT

Study investigators must follow the study protocol treatment and follow the dose reduction and adjustment guidelines in every study patient. Exceptional issues should be discussed with principal investigator. Adverse event will be documented if observed, mentioned during open questioning, or when spontaneously reported.

7.1 ADVERSE EVENT REPORTING

All Serious Adverse Events (SAEs) that occur following the subject's written consent to participate in the study through 60 days of discontinuation of dosing must be reported.

Intensity for each SAE, including any lab abnormalities, will be determined by using the NCI CTCAE version 4.0 (v4.03. June 14, 2010), as a guideline, whenever possible. The criteria are available online at http://ctep.cancer.gov/reporting/ctc.html

In this multicenter study all adverse events will be reported centrally using the accepted SAE and SUSAR report forms and CIOMS form (Appendix 7) via principal investigator Raija Silvennoinen/Helsinki University Hospital FAX number:

+358 9 471 71 897

Adverse Events

- An Adverse Event [AE] is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient or clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.
- The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AEs). The causal relationship can be one of the following:
  - Related: There is a reasonable causal relationship between study drug administration and the AE.

- Not Related: There is not a reasonable causal relationship between study drug administration and the AE.

- The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.
- Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more adverse events).

7.2 Serious Adverse Events

A **Serious Adverse Event (SAE)** is any untoward medical occurrence at any dose that:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event, defined as a medical event that may not be immediately life-threatening or result in death or hospitalization but, based on appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (eg, medical, surgical) to prevent one of the other serious outcomes listed above. Examples of such events include but are not limited to intensive treatment in an emergency department or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.

- Potential drug-induced liver injury (DILI) is also considered an important medical event--see the DILI section below for a definition of a potential DILI event.

Suspected transmission of an infectious agent (eg, pathogenic or non-pathogenic) via the study drug is an SAE.

Although pregnancy, overdose, cancer and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs.

The following hospitalizations are not considered SAEs:

- Elective surgery planned before signing consent
- Admissions as per protocol for a planned medical/surgical procedure
- Routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- Medical/surgical admission other than remedying ill health state that was planned before study entry. Appropriate documentation is required in these cases
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)

Serious Adverse Event Collecting and Reporting

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 60 days of discontinuing dosing. If applicable, SAEs must be collected that relate to any later protocol-specific procedure (such as follow-up skin biopsy).

The investigator should report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its status of seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy, or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form (CIOMS form).

SAEs, whether related or unrelated to the study drug, and pregnancies must be reported within 24 hours, SAEs must be recorded on the SAE Report Form; Pregnancies on a Pregnancy Surveillance Form (Appendix 8)

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

7.3 Health Authority Reporting (SUSAR reporting, Annual Safety reporting, any significant new observations reporting)

Investigators must adhere to local Health Authority Reporting Requirements.
The SUSARs will be reported to companies and to National Regulatory Authorities by the Sponsor-Investigator: Finnish Medicines Agency (FIMEA), Eudravigilance Database, and the appropriate Swedish Ethics Committee with CIOMS Form I.(http://www.cioms.ch/index.php/cioms-form-i).

Adverse drug reactions that are Serious, Unexpected, and at least Possibly Related to the drug (Suspected Unexpected Serious Adverse Reaction, SUSAR) and that have not previously been reported in the Investigators' Brochure, or reference safety information document will be reported promptly to the health authority in writing by the Principal Investigator.

A clear description of the suspected reaction should be provided along with an assessment as to whether the event is drug or disease related. The Principal Investigator shall notify the health authorities by fax or email of any unexpected fatal or life threatening experience associated with the use of the drugs as soon as possible but no later than 7 calendar days after initial receipt of the information. Other serious SUSARs should be reported within 15 days.

SAE´s will be reported 3 months after last study drug dose but SUSAR´s will be reported 1 year after last study drug dose.

The annual safety report (list of all suspected serious adverse reactions which have occurred during the period of time in question) will be provided to companies, Finnish Medicines Agency, Medical Products Agency (MPA) and appropriate Finnish and Swedish Ethics Committees by the Investigator-Sponsor. In Finland the annual safety report will be provided together with a brief report of the safety of persons participating in the clinical trial (signed by the person responsible for the trial).

The sponsor must without delay inform the investigators, Fimea, MPA and appropriate Ethics Committee of any significant new observations relating to the safety of the investigational medicinal product.

BMS wishes that Sponsor provides SUSARs and Annual Safety Reports, submitted to the applicable Regulatory Authorities and Ethics Committees, also to BMS either by email to worldwide.safety@bms.com or by fax to Central Facsimile Station at +1.609.818.3804. BMS wishes to receive SUSARs and

Annual Safety Reports within twenty four (24) hours of Sponsor submitting the report to the applicable Regulatory Authority and Ethics Committee.

Amgen SUSAR reporting:

When Sponsor receives a SUSAR, it shall transmit the final CIOMS report of that event to Amgen within **twenty four (24) hours** of submitting that report to the applicable regulatory authority

Amgen Global Safety:

US Toll Free fax number 1-888-814-8653
For countries where the U.S. toll-free # cannot be used: +44-20-7136-1046
Email (Only for sponsors with a secure email connection with Amgen): svc-ags-in-us@amgen.com

Non-Serious Adverse Events

A non-serious adverse event is an AE not classified as serious. Non-Serious adverse events ≥ grade 2 will be collected and reported via annual safety reports and final study reports. These AEs will be collected until 30 days after the last dose of study treatment.

Laboratory Test Abnormalities

The following laboratory abnormalities should be captured and reported as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy.

Laboratory test abnormalities are provided to AMGEN via annual safety reports (if applicable), and interim or final study reports.

7.4 PREGNANCY

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half-lives after product administration, the investigational product will be permanently

discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety).

The investigator must immediately notify the Amgen safety of this event via the Pregnancy Surveillance Form within 24 hours and in accordance with SAE reporting procedures.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on a Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported.. Information on this pregnancy may also be collected on the Pregnancy Surveillance Form.

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

7.5 OVERDOSE

Definition of overdose in this study is any accidental overdose which is overdose based on calculations of body surface are for carfilzomib or mg/kg for elotuzumab, or dose of dexamethasone which is above normal weekly dose except doses of glucocorticoid used for treat of adverse events and will be reported properly.

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as SAEs.

7.6 Potential Drug-Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event.

All occurrences of potential DILIs meeting the defined criteria must be reported as SAEs.

Potential drug induced liver injury is defined as

1. AT (ALT or AST) elevation > 3 times upper limit of normal (ULN), AND

Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase), AND

2) No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

7.7 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a nonserious or serious adverse event, as appropriate, and reported accordingly.

8. DATA MONITORING COMMITTEE

The multicenter electronic Case Report Form System, where all study data will be collected and reported, is led via Principal Investigator in Helsinki University Hospital Finland. The filled data will be followed during annual meetings of Nordic Myeloma Study Group and Finnish Myeloma Group.

Independent staff of Research Units of University Hospitals in Sweden and Finland will monitor this study at level 2. Inclusion criteria, endpoints and all key test results according to the assessment schedule will be monitored to assure data quality. The investigator is required to permit direct access to the facilities where the study took place, source documents, CRFs and applicable supporting records of subject participation for audits and inspections by Ethics Committees and

National Medicines Agency. The investigator should make every effort to be available for the audits and/or inspections

The Finnish Association of Hematology will act as an external Safety Board in this study, and all adverse events will be informed and discussed every 6-8 months. Physicians who are involved in this study are not participating in the Board.

8.1 DATA AND DOCUMENTS HANDLING

Documents which are essential for evaluation of conduct of the study and the quality of data will be filed in such a manner that they are protected from accidental loss. The sponsor-investigator will file all national essential regulatory documents relevant to the overall conduct of the trial. Local investigators will file all essential documents relevant to the conduct of the trial on site. Essential documents will be retained for 15 years after the end of the trial and the final presentation of the study. Source documents and medical records of patients should be retained for 15 years after the end of the trial. After this time these documents will be handled by the site´s guidelines regarding medical records.

8.2 AMENDMENTS

Any amendments to this protocol that seems appropriate, as the study proceeds (regarding safety, efficacy, conduction or scientific value of the study) will be agreed upon the coordinating and/or principal investigator and investigator-sponsor. Amendments will be submitted to the Ethics Committee and the regulatory authority for written approval before the implementation of the amended version. Companies will be informed about possible amendments before sending to Ethical Committee.

9. STATISTICAL CONSIDERATIONS

This is a phase 2 study with an experimental new combination for treatment of relapsed or progressive multiple myeloma. The number of patients in explorative phase 2 trials is usually from 20 to 60 patients. No formal statistical calculations or sample size determination have been performed for this pilot trial. The expected overall response rate is 70 %. With N=40 the CI95% for the expected ORR is 53-83%. The selected sample size is therefore considered adequate to rule out ORRs lower than 53%, when then observed ORR is in line with the assumption of 70 %. If the combination will fill the expectations listed in section 9.2 below the study might be expanded to include additional number of patients based on statistical power calculations.

9.1 ENDPOINT DEFINITIONS

Primary endpoint of this study is overall response rate

Secondary endpoints are

- Complete remission (CR) rate
- Quality of response (proportion of MRD negativity in patients with at least VGPR)
- Duration of responses including MRD negativity
- Progression-free survival (PFS)
- Time to next treatment (TTNT)
- Safety (Adverse events)

Minimal residual disease (MRD) will be assessed by 8-colour EuroFlow multiparameter flow cytometry if at least VGPR has been achieved.

9.2 STATISTICAL AND EFFICACY ANALYSES

Statistical analyses will be performed on intention-to-treat and on per-protocol-treated principle. Patients who have been included in the study but been withdrawn before any study drug administration are not included in analyses. Safety and efficacy analyses will be done for all patients who have received at least a single dose of study drug. Any spurious data will be abandoned. Missing

data will be handling as missing data not with replacing it with a median parameter number.

Efficacy analyses will be done using International Myeloma Working Group response criteria (Appendix 5). Response will be assessed before each cycle. Progression will be assessed using IMWG criteria for progressive disease.

For classification the adverse events NCI CTCAE version 4.0 will be used. Threshold for safety of this CAR-ELO-Dex combination is considered to be less than 70% of grade ≥ 3 non-hematological adverse events.

Efficacy, safety and QoL analysis will be performed when last patient in has been treated for two years in the study. Kaplan-Meier method will be used to estimate the time to event analyses. The PFS, TTNT and duration of response will be calculated from the start of the first dose of study drug combination.

9.3 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Baseline characteristics will include following parameters: age, sex, race, ECOG performance status, ISS stage (plasma albumin and serum-beta-2-microglobuline), paraprotein isotype, S- and U- paraprotein, S-FLC and ratio, hemoglobin, WBC, differential, platelet count, CRP, creatinine, calcium ionized, liver enzymes, LD, bone marrow morphology, bone marrow multiparameter flow cytometry, bone marrow cytogenetic analyses, FISH analyses t(4;14), +1q, cytogenetic del17p/p53 (if not previously diagnosed). Bone imaging will include skeletal ray or whole body low-dose CT, (MRI of spina and hip if clinically indicated).

10. STUDY MANAGEMENT

10.1 Compliance with the protocol

Principal investigators of each study site are responsible to follow the protocol and inform the principal investigator of whole study immediately of any possible protocol violations, any severe adverse events and any suspected unexpected

serious adverse reactions (SUSAR´s). This is mandatory because so far there are not any information or experience regarding this elotuzumab plus carfilzomib and dexamethasone treatment in MM patients. Principal investigator must confirm that any protocol revisions or amendments will be noticed and followed in each study site.

10.2 PUBLICATION

The final results of this study will be written for the publication by principal investigator and the members of the study (principal investigators and coinvestigators of sites). This study will be registered with clinicaltrials.com. and negative and inconclusive as well as positive results will be written for publication. The companies BMS and AMGEN will have possibility to review the publication three weeks before submission but the publication is owned and written by academic investigators.

10.3 DESTRUCTION OF INVESTIGATIONAL PRODUCTS

Each study site will destruct the study drugs by detailed guidelines of destruction and all procedures will be documented by pharmacy of study site.

APPENDIX 1. Eastern Cooperative Oncology Group (ECOG) Scale for Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all predisease performance without restriction
1	Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work)
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5 (6):649-55.

APPENDIX 2.

Cockcroft-Gault Equation

For males:

$$\text{Creatinine Clearance} = \frac{(140\text{-age[years]} \times \text{weight [kg]})}{72 \times (\text{serum creatinine[mg/dL]})} \text{ OR } \frac{(140\text{–age[years]} \times \text{weight [kg]})}{0.81 \times (\text{serum creatinine[}\mu\text{mol/L]})}$$

For females:

$$\text{Creatinine Clearance} = \frac{0.85\ (140\text{-age[years]} \times \text{weight [kg]})}{72 \times (\text{serum creatinine[mg/dL]})} \text{OR} \frac{0.85\ (140\text{-age[years]} \times \text{weight [kg]})}{0.81 \times (\text{serumcreatinine[}\mu\text{mol/L]})}$$

Source: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41.

APPENDIX 3.

NEW YORK HEART ASSOCIATION CLASSIFICATION OF CARDIAC DISEASE (NYHA)

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Source: The Criteria Committee of the New York Heart Association, Inc.: Diseases of the heart and blood vessels; Nomenclature and criteria for diagnosis, 6th Ed. Boston: Little, Brown; 1964.

APPENDIX 4. New international staging system (ISS) (Greipp et al. JCO 2005; 23: 3412-3420)

Stage	Criteria	Median survival months
I	Serum β_2-microglobulin < 3.5 mg/l Serum albumin ≥ 35 g/l	62
II	Not stage I or III*	44
III	Serum β_2-microglobulin ≥ 5.5 mg/l	29
* There are two categories for stage II: serum β_2-microglobulin < 3.5 mg/l but serum albumin < 35 g/l; or serum β_2-microglobulin 3.5 to 5.5 mg/l irrespective of the serum albumin level.		

APPENDIX 5. This study is for relapsed/progressed MM patients, but CRAB criteria are included as a basic information: Rajkumar SV et al. Lancet Oncol 2014;15:e538-48

Multiple myeloma
Clonal bone marrow plasma cells ≥ 10% or biopsy-proven bone or extramedullary plasmacytoma and any one or more of the following myeloma defining events • Myeloma defining events Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically: 1. Hypercalcemia: serum calcium > 0.25 mmol/l higher than the upper limit of normal or > 2.75 mmol/l 2. Renal insufficiency: creatinine clearance < 40 ml/min or serum creatinine > 177 μmol/l 3. Anemia: hemoglobin value of > 20 g/l below the lower limit of normal, or a hemoglobin value < 100 g/l 4. Bone lesions: one or more osteolytic lesions on skeletal radiography, CT or PET-CT

International Myeloma Working Group uniform response criteria by response subcategory for multiple myeloma (Rajkumar et al. Blood 2011;117(18):4691-4695)

Response	Response criteria[a]
sCR	CR as defined below plus Normal FLC ratio (0.26-1.65) and Absence of clonal cells in bone marrow[b] by immunohistochemistry or immunophenotyping[c]
CR	Negative IFE of serum and urine and Disappearance of any soft tissue plasmacytomas and < 5% plasma cells in bone marrow[b] In patients in whom the only measurable disease is by sFLC levels, CR is defined as a normal FLC ratio (0.26-1.65) in addition to the CR criteria listed above
VGPR	Serum and urine M-protein detectable by IFE but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine M-protein level < 100 mg per 24h In patients in whom the only measurable disease is by sFLC levels, VGPR is defined as a > 90% decrease in the difference between involved and uninvolved sFLC levels
PR	≥ 50% reduction of serum M-protein and reduction in 24-h urinary M-protein by ≥ 90% or to < 200mg per 24 h In patients in whom the only measurable disease is by sFLC levels, PR is defined as a ≥ 50% decrease in the difference between involved and uninvolved sFLC levels

	If serum and urine M-protein are unmeasurable, and sFLCs are also unmeasurable, ≥ 50% reduction in bone marrow plasma cells is required in place of M-protein, provided baseline percentage was ≥ 30% In addition to the above listed criteria, if present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required
SD[d]	Not meeting criteria for CR, VGPR, PR or progressive disese

Abbreviations: CR, complete response; FLC, free light chain; IFE, Immunofixation; PR, partial response; SD, stable disease; sCR, stringent complete response; VGPR, very good partial response.

[a] All response categories require two consecutive assessments made at anytime before the institution of any new therapy;
all categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed.

[b] Confirmation with repeat bone marrow examination not needed.

[c] Presence/absence of clonal cells is based upon the κ/λ ratio. An abnormal k/l ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is κ/λ of > 4:1 or < 1:2.

[d] not recommended for use as an indicator of response; stability of disease is best described by providing the time to progression estimates

NOTE: Once (s)CR is established, response remains (s)CR until relapse is documented.

RELAPSE CRITERIA

Relapse subcategory	Relapse criteria
Progressive criteria[a] To be used for calculation of time to progression and progression-free survival end points for all patients including those in CR (includes primary progressive disease and disease progression on or off therapy)	Progressive disease: requires one or more of the following: Increase of ≥ 25% from lowest response value in serum M-component (the absolute increase must be ≥ 0.5g/dl)[b] and/or Increase of ≥ 25% from lowest response value in urine M-component (the absolute increase must be ≥ 200mg/24 h) and/or In patients in whom the only measurable disease is by sFLC levels, increase of ≥ 25% from lowest response value in the difference between involved and uninvolved sFLC levels (absolute increase must be > 100 mg/L) If serum and urine M-protein are unmeasurable, and sFLC are also unmeasurable, increase of ≥ 25% from lowest response value in bone marrow plasma cell percentage (absolute % must be ≥ 10%) Definite development of new bone lesions or soft tissue plasmacytomas or definitive increase in the size of existing bone lesions or soft tissue plasmacytomas

	Development of hypercalcemia (corrected serum calcium > 11.5 mg/dl or 2.65 mmol/l) that can be attributed solely to the plasma cell proliferative disorder
Clinical relapse[a]	Clinical relapse requires one or more of: Direct indicators of increasing disease and/or end organ dysfunction (CRAB features)[b]. It is not used in calculation of time to progression or progression-free survival but is listed here as something that can be reported optionally or for use in clinical practice 1. Development of new soft tissue plasmacytomas or bone lesion 2. Definite increase in the size of existing plasma- cytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion. 3. Hypercalcaemia (> 2.65 mmol/l) (11.5 mg/dl) 4. Decrease in hemoglobin of ≥ 1.25 mmol/l (2 g/dl) 5. Rise in serum creatinine by 177 μmol/l or more (2 mg/dl or more) 6. Hyperviscosity
Relapse from CR[a] (To be used only if the end point studied is DFS)[d]	Any one or more of the following Reappearance of serum or urine M-protein by immunofixation or electrophoresis In patients in whom the only measurable disease is by sFLC levels, reappearance of abnormal sFLC levels (absolute increase must be > 100 mg/L) Development of ≥ 5% plasma cells in the bone marrow[c] Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcemia see above)

Abbreviations: CR, complete response; DFS, disease-free survival.

a All relapse categories require two consecutive assessments made at anytime before classification as relapse or disease progression and/or the institution of any new therapy.

b For progressive disease, serum M-component increases of ≥ 10 g/l are sufficient to define relapse if M-component is ≥ 50 g/l.

c Relapse from CR has the 5% cutoff versus 10% for other categories of relapse.

d For purposes of calculating time to progression and progression-free survival, CR patients should also be evaluated using criteria listed above for progressive disease

APPENDIX 6. Elotuzumab Administration Guidelines-Dose preparation, Reconstitution, Administration

Dose Preparation Instructions

After dilution in normal saline, elotuzumab infusion must be completed within 8 hours if kept at room temperature (25 °C). If a delay is anticipated after the dose has been diluted in normal saline, the prepared dose (properly identified) may be refrigerated at 2 °C to 8 °C for up to 24 hours. If stored under refrigerated conditions, the study drug solution should be equilibrated to room temperature (takes about 2 to 2.5 hours), and the container must be gently inverted to thoroughly mix the contents before administration. Do not use the accelerated warming method. If the storage time limit is exceeded, the prepared dose solution must be discarded and the reason documented by the pharmacist in the study drug accountability records.

Elotuzumab will be administered to each subject as an IV infusion, using an automated infusion pump set at the appropriate rate according to the dose administration section (see Administration Instruction section below). The dose of elotuzumab will be calculated using the subject's predose weight on Day 1 of each cycle, and then added to 0.9% saline for infusion.

Reconstitute elotuzumab lyophilized study drug, as described in steps 1 to 5.

Step 1: For a 400* mg vial of lyophilized elotuzumab, draw 17 mL of Sterile Water for Injection (SWFI), USP into a syringe equipped with an 18-gauge or smaller needle.

Step 2: Remove the flip-top from the elotuzumab vial.

Step 3: Place the vial upright on a flat surface and, using standard aseptic techniques, insert the syringe needle into the vial through the center of the rubber stopper and deliver 17 mL (into the 20-mL vial containing 400* mg elotuzumab) SWFI, USP, into the vial. Slowly remove the syringe needle out of the vial. A slight back pressure can be felt during the delivery of the SWFI into the vial, which is considered normal. The final volume of the reconstituted solution is approximately 17.6 mL, which includes the volume displaced by the solid cake. The concentration of elotuzumab in the reconstituted solution is approximately 25 mg/mL.

*400 mg is the label claim and how the vials are labeled. During the filling of the vials the manufacturer overfills the vials by 10% (40 mg) to ensure that the pharmacist can withdraw at least 400 mg. This is a standard practice for injectable products because it is not possible to withdraw the entire contents from the vial.

Step 4: Hold the vial upright and gently swirl the solution by rotating the vial to dissolve the lyophilized cake. Then gently invert the vial a few times in order to dissolve any powder that may be present on top of the vial or the stopper. Finally, hold the vial upright again and gently swirl the solution a few more times to dissolve any remaining particles. Avoid prolonged or vigorous agitation. DO NOT SHAKE.

Step 5: After the remaining solids are completely dissolved, allow the reconstituted solution to stand for 5 to 10 minutes.

It is acceptable to have small bubbles and/or foam around the edge of the vial. The reconstituted preparation results in a colorless to slightly yellow, clear to slightly opalescent solution containing approximately 25 mg/mL of elotuzumab.

Step 6: Once the reconstitution is completed, withdraw the calculated drug volume and further dilute with 230mL normal saline into an infusion bag. Elotuzumab solutions are compatible with polyvinyl chloride and

polyolefin bags. Examples of such bags include Viaflo, MacoPharma Easyflex N, Macoflex N, B Braun Excel, and Braun Ecobag.

Drug volume will be calculated based on subject weight: For example, a subject receiving 10 mg/kg elotuzumab who weighs 80 kg on Day 1 [predose] will require 800 mg of study drug for infusion. Withdraw 32 mL of elotuzumab (25 mg/mL) from 2 vials and add to an infusion bag already containing 230 mL saline, for a total of 262 mL to be infused.

Use a new sterile needle for withdrawing solution from each vial.

The same vial must not be used to prepare elotuzumab for more than one subject. Used elotuzumab vials will be stored until study drug accountability has been completed by the BMS designee, and destruction or return is authorized. Used vials do not need to be refrigerated.

Administration Instructions:

1. Administer through a low-protein-binding 0.22 - micrometer or smaller in-line filter (placed as proximal to the subject as is practical). Prime the infusion line with study drug before starting the infusion.
2. Set the IV pump to deliver the infusion at the rate of 0.5 mL per minute (including the drug in the line). The total time of infusion will vary depending upon the maximum tolerated mL/min infusion rate as discussed above.
3. Record every time the infusion is started and stopped and the reason why the start and stop occurred.
4. Monitor the IV setup and the subject's IV site frequently during infusion, checking for the correct infusion rate and IV site infiltration.
5. Ensure that the full volume of elotuzumab is infused.
6. After elotuzumab has been infused from the line, discontinue the infusion, disconnect the IV tubing, and dispose of materials appropriately according to the facility's standard procedure.

Serious Adverse Event Report

1(1)

Study name / code: KEd NMSG#24/15

EudraCT number: 2016-001176-13

Study site:

Principal investigator:

Report type: Initial ☐ Follow-up ☐

I Reaction information

SUBJECT NUMBER	DATE OF BIRTH (dd.mm.yyyy)	AGE (y)	SEX	ONSET DATE (dd.mm.yyyy)	END DATE (dd.mm.yyyy / ongoing)	CHECK ALL APPROPRIATE TO ADVERSE REACTION
						☐ Patient died

EVENT DESCRIPTION (including relevant tests / lab data)

☐ Life threatening

☐ Involved or prolonged inpatient hospitalisation

☐ Involved persistent or significant disability or incapacity

☐ Congenital anomaly

☐ Other medically important condition

OUTCOME OF SAE

Resolved	Resolved with sequela	Ongoing	Fatal	Unknown / Lost to follow-up
☐	☐	☐	☐	☐

II Suspect drug(s) information

SUSPECT DRUG (Include generic name)

Did reaction abate after stopping drug?

Yes	No	NA
☐	☐	☐

DAILY DOSE(S)

ROUTE(S) OF ADMINISTRATION

INDICATION(S) FOR USE

Did reaction reappear after reintroduction?

Yes	No	NA
☐	☐	☐

THERAPY DATES (dd.mm.yyyy) — from: — to:

THERAPY DURATION

Was the blinding code broken?

Yes	No	NA
☐	☐	☐

III Concomitant medication and history

CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (excluding those used to treat reaction)

OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period etc.)

Causality

Probable	Possible	Unlikely
☐	☐	☐

SUSAR (Suspected Unexpected Serious Adverse Reaction)

Yes	No
☐	☐

Name of reporter and role in study _____ Date _____ Signature _____

Version 1.11.2017

Suspected Unexpected Serious Adverse Reaction Report

1(1)

Study name / code: KEd NMSG#24/15

EudraCT-number: 2016-001178-13

Study site:

Principal Investigator:

I Reaction information

SUBJECT NUMBER	DATE OF BIRTH (dd.mm.yyyy)	AGE (y)	SEX	ONSET DATE (dd.mm.yyyy)	END DATE (dd.mm.yyyy / ongoing)	CHECK ALL APPROPRIATE TO ADVERSE REACTION
						☐ Patient died

EVENT DESCRIPTION (including relevant tests / lab data)

☐ Life threatening

☐ Involved or prolonged inpatient hospitalisation

☐ Involved persistence or significant disability or incapacity

☐ Congenital anomaly

OUTCOME OF EVENT

Resolved	Resolved with sequela	Ongoing	Fatal	Unknown / Lost to follow-up
☐	☐	☐	☐	☐

☐ Other medically important condition _____

II Suspect drug(s) information

SUSPECT DRUG (include generic name and manufacturer)

Did reaction abate after stopping drug?

Yes	No	NA
☐	☐	☐

DAILY DOSE(S)	
ROUTE(S) OF ADMINISTRATION	
INDICATION(S) FOR USE	

Did reaction reappear after reintroduction?

Yes	No	NA
☐	☐	☐

THERAPY DATES	from: (dd.mm.yyyy)	to: (dd.mm.yyyy)	THERAPY DURATION	

III Concomitant medication and history

CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (excluding those used to treat reaction)	OTHER RELEVANT HISTORY (e.g. diagnostics, allergies, pregnancy with last month of period etc.)

Report type: Initial ☐ Follow-up ☐

Name of reporter and role in study _____ Date _____ Signature _____

Version 1.11.2017

CIOMS FORM

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE Years	3. SEX	4-6 REACTION ONSET Day	Month	Year	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)										☐ PATIENT DIED ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION ☐ INVOLVED PERSISTENCE OR SIGNIFICANT DISABILITY OR INCAPACITY ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)		20 DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☐ NA
15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☐ NA
17. INDICATION(S) FOR USE		
18. THERAPY DATES (from/to)	19. THERAPY DURATION	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER		
	24b. MFR CONTROL NO.	
24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL	
DATE OF THIS REPORT	25a. REPORT TYPE ☐ INITIAL ☐ FOLLOWUP	

Appendix 8 Pregnancy Surveillance Form (Different attachment)

REFERENCES

1. Attal M et al. Autologous Transplantation for Multiple Myeloma in the Era of New Drugs: A Phase III Study of the Intergroupe Francophone Du Myelome (IFM/DFCI 2009 Trial) Abstract#391. ASH 2015.
2. Bakkus MH, Bouko Y, Samson D et al. Post-transplantation tumour load in bone marrow, as assessed by quantitative ASO-PCR, is a prognostic parameter in multiple myeloma. Br J Haematol 2004;126:665-674.
3. Berenson J, Cartmell A, Lyons R et al. Weekly carfilzomib with dexamethasone for patients with relapsed or refractory multiple myeloma: Updated results from the Phase 1/2 study Champion-1 (NCT01677858). ASH 2015 abstract # 373.
4. Bergsagel PL. Where we were, where we are, where we ar going: Progress in multiple myeloma. Asco.org/edbook. 2014 ASCO Educational Book.
5. Bird JM, Owen RG, D´Sa S et al. Guidelines for the diagnosis and management of multiple myeloma. Br J Haemat 2011;154:32-75
6. Chng WJ, Dispenzieri A, Chim C-S, Fonseca R, Goldschmidt H, Lentzsch S et al. IMWG consensus on risk stratification in multiple myeloma, Leukemia 2014;28:269-277.
7. CTCAE, Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (v4.03.June 14, 2010).
8. Dimopoulos MA, Moreau P, Palumbo A, Joshua D, Pour L, Hájek R, et al. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomized, phase 3, open-label, multicenter study. Lancet Oncol 2016 ;17:27-38.
9. Engelhardt M, Terpos E, Kleber M et al. European Myeloma Network recommendations on the evaluation and treatment of newly diagnosed patients with multiple myeloma. Haematologica 2014;99(2):232-242.
10. Engholm G, Ferlay J, Christensen N, Kejs AMT, Johannesen TB, Khan S, Leinonen M, Milter MC, Ólafsdóttir E, Petersen T, Stenz F, Storm HH. NORDCAN: Cancer Incidence, Mortality, Prevalence and Survival in the Nordic Countries, Version 7.1 (09.07.2015). Association of the Nordic Cancer Registries. Danish Cancer Society. Available from http://www.ancr.nu, accessed on day/month/year.
11. Investigator brochure elotuzumab BMS-901608. Version no.11. Version date:10-Aug-2015.
12. Jakubowiak AJ et al. A phase 1/2 study of carfilzomib in combination with lenalidomide and low-dose dexamethasone as a frontline treatment for multiple myeloma. Blood 2012;120:1801-1809.
13. Jakubowiak AJ. Evolution of carfilzomib dose and schedule in patients with multiple myeloma: a historical overview. Cancer

Treat Rev.2014;40:781-790.
14. Ladetto M, Bruggemann M, Montillo L et al. Next-generation sequencing and real-time quantitative PCR for minimal residual disease detection in B-cell disorders. Leukemia 2014;28:1299-1307.
15. Ladetto M, Pagliano G, Ferrero S et al. Major tumor shrinking and persistent molecular remissions after consolidation with bortezomib, thalidomide and dexamethasone in patients with autografted myeloma. J Clin Oncol 2010;28:2077-2084
16. Lonial S, Dimopoulos M, Palumbo A, et al. Elotuzumab therapy for relapsed or refractory multiple myeloma. N Engl J Med. 2015;373:621-631.
17. Martinez-Lopez J, Lahuerta JJ, Pepin F et al. Prognostic value of deep sequencing method for minimal residual disease detection in multiple myeloma. Blood 2014;123:3073-3079.
18. Muchtar E, Gertz MA, Magen H. A practical review on carfilzomib in multiple myeloma. Eur J Haematol. 2016 Feb 19. Doi:10.1111/ejh.12749 [Epub ahead of print] Review.
19. Montero-Flores J, Tute de R, Paiva B et al. Immunophenotype of normal vs. myeloma plasma cells: Toward antibody panel specifications for MRD detection in multiple myeloma. Cytometry Part B (Clinical Cytometry) 00B:00-00 (2015) DOI: 10.1002/cyto.b.21265.
20. Moreau P, Masszi T, Grzasko N et al. Ixazomib, an Investigational Oral Proteasome Inhibitor (PI), in Combination with Lenalidomide and Dexamethasone (IRd), Significantly Extends Progression-Free Survival (PFS) for Patients (Pts) with Relapsed and/or Refractory Multiple Myeloma (RRMM): The Phase 3 Tourmaline-MM1 Study (NCT01564537). Blood 2015;126:727.
21. Nahi H, Våtsveen TK, Lund J, Heeg BM, Preiss B, Alici E et al. Proteasome inhibitors and IMiDs can overcome some high risk cytogenetics in multiple myeloma but not gain 1q21. Eur J Haemat 2015 Mar 16. Doi:10.1111/ejh.12546.
22. Niesvizky R, Martin TG, Bensinger WI et al. Dose-escalation study (PX-171-006) of carfilzomib, lenalidomide and low-dose dexamethasone in relapsed or progressive multiple myeloma. Clin Cancer Res 2013;19:2248-2256.
23. Paiva B, Puig N, Garcia-Sanz R, San Miguel JF. Is this the time to introduce minimal residual disease in multiple myeloma clinical practice? Clin Cancer Res;21(9) May 1,2015
24. Paiva B, van Dongen JJM, Orfao A. New criteria for response assessment: role of minimal residual disease in multiple myeloma. Blood 2015;125(20):3059-3068.
25. Palumbo A, Offidano M, Pégourie B, De La Rubia J, Garderet L, Laribi K, et al. Elotuzumab plus bortezomib and dexamethasone versus bortezomib and dexamethasone in patients with relapsed/refractory multiple myeloma: 2 –year follow-up. Blood 2015;126:510.
26. Puig N, Sarasquete ME, Balanzategui A et al. Critical evaluation

of ASO RQ-PCR for minimal residual disease evaluation in multiple myeloma. A comparative analysis with flow cytometry. Leukemia 2014;28:391-397.

27. Rajkumar SV, Harousseau L, Durie B et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. Blood 2011;117:4691-4695.
28. Rajkumar SV. Myeloma today: Disease definitions and treatment advances. Am J Hematol 2016;91:90-100.
29. Rawstron AC, Child JA, de Tute RM et al. Minimal residual disease assessed by multiparameter flow cytometry in multiple myeloma: impact on outcome in the Medical Research Council Myeloma IX Study. J Clin Oncol 2013;31:2540-2547.
30. Rawstron AC, Orfao A, Beksac M et al. Report of the European Myeloma Network on multiparametric flow cytometry in multiple myeloma and related disorders. Haematologica 2008;93:431-438.
31. Rawstron AC, Paiva B, Stetler-Stevenson M. Assessment of minimal residual disease in myeloma and the need for a consensus approach. Cytometry B Clin Cytom. 2016;90:21-25.
32. Ross et al. Report from the European Myeloma Network on interphase FISH in multiple myeloma and related disorders. Haematologica 2012;97:1272-1277.
33. San Miguel J, Weisel K, Moreau P et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): A randomized, open-label, phase 3 trial. Lancet Oncol 2013;14:1055-1066.
34. San Miguel JF, Hungria VT, Yoon SS et al. Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicenter, randomized, double-blind phase 3 trial. Lancet Oncol 2014;15:1195-1206
35. Siegel DS, Martin T, Wang M et al. A phase 2 study of single-agent carfilzomib (PX-171-003-A1) in patients with relapsed and refractory multiple myeloma. Blood 2012;120:2817-2815.
36. Silvennoinen R, Lundan T, Kairisto V et al. Comparative analysis of minimal residual disease detection by multiparameter flow cytometry and enhanced ASO RQ-PCR in multiple myeloma. Blood Cancer J 2014;4:e250.
37. Stetler-Stevenson M, Paiva B, Stoolman L et al. Consensus guidelines for myeloma minimal residual disease sample staining and data acquisition. Cytometry Part B Clinical Cytometry 2016;90:26-30.
38. Stewart AK, Rajkumar SV, Dimopoulos Ma et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. N Engl J Med 2015 Jan;372(2):142-152.
39. Van de Velde HJK, Liu X, Chen G, Cakana A, Draedt W, Bayssas M. Complete response correlates with long-term survival and progression-free survival in high-dose therapy in multiple

myeloma. Haematologica 2007;92:1399–1406.

40. van Dongen JJ, Lhermitte L, Böttcher S et al. EuroFlow Consortium (EU-FP6, LSHB-CT-2006-018708). EuroFlow antibody panels for standardized n-dimensional flow cytometric immunophenotyping of normal, reactive and

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