CLINICAL STUDY PROTOCOL

NMSG25/16 – THE CONPET STUDY

KRd consolidation in myeloma patients with a positive PET-CT after standard first line treatment. A phase II study

Indication: **PET-positivity after standard first line treatment**
Phase: **Phase 2**

Protocol history **Original**

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Principal Investigator signature page

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Local Investigator:_____

Signature of Investigator

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Printed name of Investigator

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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: KRd consolidation in myeloma patients with a positive PET-CT after standard first line treatment – The CONPET study

Design: An investigator initiated, academic, non-randomized, open-label multicenter phase 2 study that will assess carfilzomib, lenalidomide and dexamethasone regimen as treatment consolidation in patients with multiple myeloma who are PET-CT positive after standard first line treatment in patients fit for autologous transplant.

Patient Population

Multiple myeloma patients treated with standard first line therapy with or without ASCT who have achieved at least very good partial remission.

Number of Patients: 50 patients with PET-CT positivity after standard first line therapy

Participating centers: Oslo, Odense, Copenhagen, Lund, Vejle

Study Objectives

Primary

- To assess the proportion of patients that are PET-positive after standard first line treatment, and how many of these can become PET-negative after 4 cycles of KRd consolidation.

Secondary

- The correspondence between PET-CT results and MRD dynamics by intra-patient comparison.

Study Endpoints

Primary:

- Proportion of PET-CT positivity after standard first line therapy
- Change from PET-CT positivity to PET-CT negativity after 4 cycles of KRd consolidation.

Secondary:

- MRD negativity by 8-colour EuroFlow after 4 cycles of KRD consolidation.
- Safety
- Overall response rate
- Progression-free survival (PFS)
- Time to next treatment (TTNT)
- Overall survival (OS)
- Quality of life during and after KRD consolidation

Treatment schedule

Four cycles of Carfilzomib-Lenalidomide-Dexamethason

The carfilzomib dose is 20-20-36-36-36-36 mg/m^2 on day 1, 2, 8, 9, 15 and 16 in the first cycle. It will be increased to 36 mg/m^2 on days 1, 2, 8, 9, 15 and 16 in cycles 2-4.

The oral dexamethasone dose is 40 mg weekly throughout the study for patients under 75 years of age. 20 mg for patients over 75 years of age.

The Revlimid dose is 25 mg on days 1-21 in every cycle.

Inclusion criteria (selected)

1. Prior confirmed diagnosis of multiple myeloma (2014).
2. Received standard first line treatment with at least partial response. Standard first line treatment is defined as VRD, VTD or VCD followed by ASCT, with or without lenalidomide maintenance
3. Carfilzomib naïve
4. Eastern Cooperative Oncology Group (ECOG) performance status 0-2.
5. Absolute neutrophil count (ANC) $\geq$ 0,5 x 10^9/L) and platelet count >35 x 10^9/L.
6. At least very good partial remission (VGPR) from first line treatment

Exclusion criteria (selected)

1. Change of first line treatment because of stabile or progressive disease.
2. Major surgery within 28 days before enrollment.
3. Radiotherapy within 14 days before enrollment.
4. Glucocorticoid therapy within the 14 days prior to inclusion that exceeds a cumulative dose of 160 mg dexamethasone or 1000 mg prednisone.
5. Patients who started treatment more than 12 month before screening
6. Central nervous system involvement.
7. Uncontrolled heart disease, including congestive heart failure (NYHA III-IV), uncontrolled angina pectoris, uncontrolled conduction abnormalities, acute diffuse infiltrative pulmonary disease, pericardial disease or myocardial infarction within 6 months prior to enrollment
8. Uncontrolled hypertension or uncontrolled diabetes despite medication
9. Active hepatitis B or C infection or known human immunodeficiency virus (HIV) positivity.
10. Another active malignancy. Patients with non-melanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.
11. Primary plasma cell leukemia, systemic AL amyloidosis, Waldenströms macroglobulinemia, POEMS syndrome
12. Not expected to tolerate full dose KRd

Duration of Study:

Expected duration of treatment:

- Patient recruitment 24 months
- Study duration until progressive disease in all patients
- Primary endpoint together with the relevant secondary endpoints will be assessed after the minimum follow-up of three months after completed treatment for the last included patient.
- The patients will be followed until death or loss to follow-up.
- Expected start-up is August 2017
- Primary results will be evaluated after last patient has performed KRd treatment.

Abbreviation	Definition
AE	adverse events
AML	acute myeloid leukemia
ANC	absolute neutrophil count
ASCT	autologous stem cell transfer
AUC	area under the curve
BM	bone marrow
Cmax	maximum serum concentration of a drug in a specified compartment
CR	complete response
CTCAE	common terminology criteria for adverse events
ECG	electrocardiography
eCRF	electronic case report form
ECOG	eastern cooperative oncology group
EOT	end of treatment
18F-FDG	2-deoxy-2[fluorine-18]fluoro- D-glucose
FCBPs	females of childbearing potential
IHC-GCP	the international conference on harmonization's guideline for good clinical practice
ISS	international staging system
IMWG	international myeloma working group
KRd	carfilzomib lenalidomide dexamethasone
MDS	myelodysplastic syndrome
MFC	multiparameter flow cytometry
MM	multiple myeloma
MPV	melphalan prednisolone bortezomib
MRD	minimal residual disease
MRI	magnetic resonance imaging
NDMM	newly diagnosed multiple myeloma
ORR	overall response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PET-CT	positron emission tomography-computed tomography
PFS	progression-free survival
PI	proteasome inhibitor
PO	per oral
PR	partial response
QOL-forms	quality of life questionnaire forms
Rd	lenalidomide dexamethasone
REK	the regional ethics committee
SAE	serious adverse advent
SD	stable disease
sFLC	serum free light chain
SJS	stevens-johnson syndrome
SPMs	second primary malignancies
SUSAR	suspected unexpected severe adverse event
TEN	toxic epidermal necrolysis

TTNT	time to next treatment
VCD	bortezomib cyclophosphamide dexamethasone
VGPR	very good partial response
VRD	bortezomib lenalidomide dexamethasone
VTD	bortezomib thalidomide dexamethasone
VTE	deep vein thrombosis

STUDY PROCEDURES

	Screening (Day -28-0	Day 1 Cycle 1	Day 15 Cycle 1-4	Day 1 Cycle 2-4	Day 2, 8, 9, 15,16 Cycle 1-4	Visit D1 C4D29 +/- 2 days	Visit D2 one month after D1 +/- 2 days	Every second months +/- 7 days	EOT at PD	Every 3m after PD until death
Medical/treatment history	X									
Complete physical examination, including height	X									
Targeted physical examination		X		X	X	X	X	X	X	
Vital Signs[a]	X	X		X	X	X				
Hematology[b]	X	X	X	X		X	X	X	X	
Comprehensive blood chemistry panel[c]	X	X		X		X	X	X	X	
Evaluation of clonal disease[d]	X	X		X		X	X	X	X	
Safety assessment, AEs	X	X		X	X	X	X	X	X	
Targeted neurologic evaluation	X	X		X	X	X	X	X	X	
Quality of life evaluation		X	X	X		X	X		X	
BM aspiration for MRD Euroflow		X				X				
PET-CT	X						X			
ECG	X									
ECHO cor, if clinically indicated	X									
Pregnancy test in fertile women	X	X		X		X	X	X	X	
Use of diuretics	X	X		X	X	X				
Overall survival		X		X	X	X	X	X	X	X

[a] Heart rate, blood pressure, temperature, weight

[b] Neutrophils, hemoglobin, platelets

[c] Hematology, SR, CRP, Potassium, Sodium, Total calcium, ionized calcium, magnesium, phosphate, creatinine, estimated GFR, ASAT, ALAT, gGT, ALP, LD Trop T, Pro-BNP, Bilirubin, Glucose, Albumin, Total protein, Uric acid

[d] Serum and urine electrophoresis with immune fixation; serum free light chains; bone marrow aspirate/biopsy if CR/sCR is suspected from last visit

Introduction

INTRODUCTION

1.1 Scientific background

Multiple myeloma (MM) is the most common hematological malignancy after lymphomas. 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 (1). High-dose therapy supported by ASCT is the standard first-line therapy for MM in eligible patients under 65 (-70) years, whereas bortezomib and/or lenalidomide based treatments is the standard choice for patients not eligible for ASCT.

In the ASCT eligible patients, the consensus for induction treatment is a triple combination of proteasome inhibitor (PI) plus immunomodulatory or an alkylating agent with dexamethasone for 3-4 cycles. Common regimes in the Nordic countries are VCD and VTD, with rare examples of VRD use. In the non-ASCT-eligible patients, MPV and Rd are the preferred choices, with increasing interest in the VRD regime. At relapse, Rd is the most common choice in most situations, with an exception for relapse after Rd, where Vd often is preferred. Recently, carfilzomib has been approved in this setting, in combination with Rd, but reimbursement is still varied between countries. Most patients relapse after first-line therapy, and there may be several relapses in the course of the disease. Time to first relapse is an important predictor for overall survival.

At ASH 2015, an IFM study was presented showing that PET-CT before maintenance after first-line treatment was the best predictor for overall survival (Moreau et al, ASH 2015, abstract 395). These patients are therefore the focus of this study.

1.2 MRD measurement

Both multiparameter flow cytometry (MFC) and next generation sequencing (NGS) have been used in MM to assess MRD. MFC 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 (2). Consensus guidelines for MFC-MRD sample processing and MRD detection has now been published (Rawstron et al. 2016). In practice, MFC is the most practical and fastest method for MRD assessment, and will be used in this study (3). The standard Euroflow setup will be used.

1. STUDY DRUGS

2.1 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 (4). 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 several treatment lines in the era of novel drugs. However, it has a high incidence of peripheral neuropathy causing cessation of treatment in a significant proportion of patients, and resistance development will eventually occur in most patients. The side effect profile of carfilzomib is milder than with bortezomib, and especially the incidence of neuropathy is significantly lower (5). The most common side effects are thrombocytopenia and anemia, fatigue, nausea, dyspnea, diarrhea and pyrexia (incidence ≥ 30%). However, most of these side effects are mild and only the cytopenias were of grade 3 or 4 in more than 10% of the patients in published studies. Some rare and severe side effects have been observed in phase 2 trials. Cardiac failure events (e.g. cardiac failure, pulmonary edema, decreased ejection fraction) 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 the 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 (6). 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 (7). 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 combination of CAR + LEN + Dex was compared with LEN + DEX in 792 patients with relapsed myeloma (5). 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. In the other phase 3 trial (ENDEAVOR) CAR + Dex was compared with bortezomib + Dex in relapsed or refractory myeloma (8). Again, combination of carfilzomib was more efficient: objective responses were observed in 77 % vs 63 %, and complete responses in 13 % vs 6 %. Moreover, median PFS was 18.7 vs 11.1 months ($p<0.0001$). 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 (9). 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 was 27 mg/m^2 whereas in the ENDEAVOR study with only dexamethasone added, a dose of 56 mg/m^2 was used with acceptable toxicity.

2.1.1 Carfilzomib dosing in this study

There are four phase 3 studies in multiple myeloma, three for relapsed/refractory patients: ASPIRE (NCT01080391, PX-171-009)(5), FOCUS (NCT01302392, PX-171-011)(4), ENDEAVOR (NCT01568866, 2011-003)(8) 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 (10).

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 (11). 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 and 70 mg/m^2. Carfilzomib was administered 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, where the majority of patients were IMiD and bortezomib refractory, was 23.7% (7). With 56 mg/m^2, ORR was 50% in a 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 led to the study CHAMPION-1 were higher once weekly dosing of carfilzomib was investigated.

In CHAMPION-1, a phase 1b/2 study for relapsed MM patients with 1-3 prior therapies, the dose-escalation part 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 (10). 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 the expansion cohort, one additional grade 3 dyspnea was noticed. The MTD of once-weekly carfilzomib combined with dexamethasone was determined to be 70 mg/m^2. The CHAMPION-1

study 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; nausea and diarrhea (35%) the most common non-hematological 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. Three grade five SAEs were reported in three patients; acute renal failure, cardio-respiratory arrest and disease progression. The preliminary results of the 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. This has led to the ARROW phase three study where once-weekly carfilzomib 70 mg/m^2 is compared to 20/27 mg/m^2 twice-weekly dosing with superiority design.

In addition, published studies have shown sufficient safety with up to 24 cycles of KRd in NDMM patients, giving reasonable evidence for the safety of this study design (12).

2.1.1.1 KRd with 20/36mg/m^2

In randomised trials, KRd has been given with a carfilzomib dose of 27mg/m^2. This has however been in relapsed patients with long-term treatment. In newly diagnosed patients, phase-2-studies has evaluated the higher dose of 36mg/m^2, both for a shorter time (8 cycles) (13) and for longer time (up to 25 cycles) (14). In the study with most prolonged treatment, there was a phase 1-2 dose finding study. There was no maximum tolerated dose, but from efficacy and safety perspectives, the dose of 36mg/m^2 was chosen. In both studies, the standard administration of lenalidomide 25mg days 1-21 and dexamethasone 40mg weekly was used.

Hence, the experience in newly diagnosed multiple myeloma, also for prolonged treatment, is largest with the dose 20/36mg/m^2, and standard LenDex administration. This was chosen as the regime in our study. The choice of 4 cycles is a medium sized number of consolidation cycles, and is chosen after discussions with experts in the field (Jens Hillengass, Xavier Leleu), trying to balance the need for efficacy without the intent of a short time intervention.

2.1.2 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 (15). 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 for twice-weekly 20/27 mg/m^2 dosing. 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 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 (15). 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.

2.2 Rationale for the Use of Lenalidomide in Combination with Low-Dose Dexamethasone and Carfilzomib

IMiDs (Thalidomide, Lenalidomide, and Pomalidomide), also known as immunomodulatory agents, are a backbone in myeloma therapy and have been rationally combined with proteasome inhibitors for several years. After the ASPIRE trial mentioned previously, the combination with carfilzomib and low-dose dexamethasone have become a standard-of-care for myeloma patients in first relapse, and is therefore a logical choice as consolidation in patients who have not received at least either carfilzomib or lenalidomide (5).

2.3 Lenalidomide

Lenalidomide is a thalidomide analogue, an immunomodulatory agent with anti-angiogenic properties. The chemical name is 3-(4-amino-1,3-dihydro-1-oxo- 2H-isoindol-2-yl) piperidine-2,6-dione. Lenalidomide is rapidly absorbed under fasting condition following oral administration, with the Cmax in plasma usually occurring at a median time of approximately 0.5 and 1.5 hours post dose. In the pivotal efficacy and safety MM registration trials the drug was administered without regard to food

intake. Thus, lenalidomide can be administered with or without food. Lenalidomide is not a substrate of hepatic metabolic enzymes in vitro and metabolism contributes to a very minor extent to the systemic clearance of lenalidomide in humans. Lenalidomide is eliminated predominantly through renal excretion of the unchanged drug. Approximately 65%-85% of the administered dose is excreted in urine in unchanged drug. The elimination half-life is appr. 3 to 5 hours at the clinically relevant doses. Steady-state levels are achieved within 4 days. Lenalidomide is not expected to affect dexamethasone metabolism because lenalidomide is not an inducer of the human CYP enzyme. P-gp does not play an important role in pharmacokinetics of lenalidomide in humans.

The identified AEs associated with the use of lenalidomide across all studied indications are commonly related to the blood and lymphatic systems, gastrointestinal disorders, infections and infestations, skin and subcutaneous tissue disorders, and vascular disorders. The most serious adverse reactions are venous thromboembolism (deep vein thrombosis, pulmonary embolism) and grade 4 neutropenia.

The most frequently observed adverse reactions which occurred significantly more frequently in the lenalidomide/dexamethasone group compared to the placebo/dexamethasone group were neutropenia (39.4%), fatigue (27.2%), asthenia (17.6%), constipation (23.5%), muscle cramp (20.1%), thrombocytopenia (18.4%), anaemia (17.0%), diarrhea (14.2%) and rash (10.2%).

Hematological toxicity: Neutropenia and thrombocytopenia: Lenalidomide is associated with anemia, neutropenia, febrile neutropenia, thrombocytopenia and pancytopenia. Grade 3 or 4 neutropenia and thrombocytopenia are the most common dose-limiting AEs. A complete blood cell count, including WBC count with differential, platelet count, hemoglobin and haematocrit, should be performed to monitor for cytopenias in accordance with the protocol during the study and cytopenias should be handled by protocol guidelines. Patients with neutropenia should be monitored for signs of infection. Patients and physicians are advised to be observant for signs and symptoms of bleeding, including petechiae and epistaxis, especially in case of concomitant medication susceptible to induce bleeding, a dose reduction of lenalidomide may be required.

Gastrointestinal disorders: Constipation, diarrhea, nausea, and vomiting were the most commonly reported gastrointestinal AEs during treatment with lenalidomide.

Hepatic disorders: Cases of transient liver laboratory abnormalities, predominantly transaminases, were reported in patients treated with lenalidomide. Treatment with lenalidomide should be interrupted and restarted once the levels return to baseline. Successful rechallenge without recurrence of liver laboratory elevations was reported in some patients. In post-marketing surveillance, a few cases of acute hepatic failure, including fatalities, were reported. The mechanism of reported hepatic toxicity remain unknown although, in some cases, pre-existing viral liver disease, elevated baseline liver enzymes, and possibly treatment with antibiotics might be risk factors.

Infections and infestations: Treatment-emergent AEs of infections, specifically pneumonia, are commonly seen with lenalidomide.

Cardiac disorders: Adverse events such as atrial fibrillation, myocardial infarction and heart failure have been reported with the use of lenalidomide from clinical studies and post-marketing surveillance. Patients with prior history and known risk factors for these AEs should be closely monitored.

Venous and arterial thromboembolic events: There is an increased risk of VTEs (predominantly deep vein thrombosis and pulmonary embolism) in MM patients treated with lenalidomide in combination with dexamethasone or other chemotherapy. There is also an increased risk of arterial thromboembolic events (predominantly myocardial infarction and cerebrovascular event). Patients with known risk factors for thromboembolism- including prior thrombosis- should be closely monitored. Action should be taken to try to minimize all modifiable risk factors (e.g. smoking, hypertension, hyperlipidemia). Erythropoietin agents and hormone-replacement therapy should be used with caution in patients receiving lenalidomide and dexamethasone. Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, arm or leg swelling.

If the patient experiences any thromboembolic events, treatment must be discontinued, and standard anticoagulation therapy started. Once the patient has been stabilized on the anticoagulation treatment and any complications of the thromboembolic event have been managed, the lenalidomide treatment may be restarted at the original dose dependent upon a benefit risk assessment. The patient should continue anticoagulation therapy during the course of lenalidomide treatment.

Renal impairment: Since lenalidomide is primarily excreted unchanged by the kidney, starting dose adjustments is recommended in patients with renal impairment. Therefore, care should be taken in dose selection and monitoring of renal function is advised in patients with renal impairment.

Thyroid function: Cases of hypothyroidism and thyroid dysfunction have been reported and monitoring of thyroid function should be considered.

Peripheral neuropathy: Lenalidomide is structurally related to thalidomide, which is known to induce severe peripheral neuropathy. At this time, the neurotoxic potential of lenalidomide associated with long-term use cannot be ruled out.

Tumour Lysis Syndrome: Because lenalidomide has anti-neoplastic activity the complications of tumour lysis syndrome may occur. The patients at risk of tumour lysis syndrome are those with high tumour burden prior to treatment. These patients should be monitored closely, and appropriate precautions taken.

Allergic Reactions: Cases of allergic reaction/hypersensitivity reactions have been reported.

Severe skin reactions: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported. Lenalidomide must be discontinued for angioedema, grade 4 rash, exfoliative or bullous rash, or if SJS or TEN is suspected, and should not be resumed following discontinuation for these reactions. Discontinuation of lenalidomide should be considered if skin rash $\geq$ grade 2 is exfoliative or bullous or if SJS or TEN is suspected. for other forms of skin Lenalidomide should not be resumed following discontinuation for these reactions.

Musculoskeletal and connective tissue disorders: The rare AE of rhabdomyolysis has been observed with lenalidomide. The reports of rhabdomyolysis were confounded by concurrent use of statins and dexamethasone, concurrent viral and bacterial infections, trauma, and serotonin syndrome, which are risk factors for rhabdomyolysis.

Neoplasms benign, malignant and unspecified. Second primary malignancies: NDMM: In clinical trials of NDMM an increase of invasive SPMs, most notably AML and MDS, has been observed predominantly in subjects receiving lenalidomide in combination with melphalan or immediately following high-dose melphalan and ASCT. The incidence rate was 1.57 per 100 person-years for the combined MPR arms and 0.36 per 100 person-years for the MP+p control arm. Cases of B-cell malignancies were observed in clinical trials where subjects received lenalidomide in

the post-ASCT setting. Patients should be carefully evaluated before and during treatment using standard cancer screening for occurrence of SPMs, and treatment should be instituted as appropriate.

Post-marketing data: Pneumonitis, transient abnormal liver laboratory tests, hyperthyroidism, hypothyroidism, TLS, TFR and allergic conditions including angioedema, SJS and TEN have been identified and are considered by Celgene to be at least possibly related to lenalidomide.

Lactose intolerance: Revlimid capsules contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Unused capsules: Patients should be advised never to give this medicinal product to another person and to return any unused capsules to their pharmacist at the end of the treatment.

Lenalidomide is not a substrate of CYP enzymes in vitro, is a weak substrate but not an inhibitor of P-gp. Lenalidomide and concomitant digoxin: Concomitant administration with lenalidomide 10mg/day increased the plasma exposure of digoxin by 14%. Periodic monitoring of digoxin levels in patients receiving concomitant lenalidomide is recommended based on standard clinical practice. Lenalidomide and concomitant warfarin: Monitoring of warfarin concentration in accordance with standard practice is advised during treatment with lenalidomide.

Because of the increased risk of venous thromboembolism in subjects with multiple myeloma taking lenalidomide and dexamethasone, combined oral contraceptive pills are not recommended. If a subject is currently using combined oral contraception the subject should switch to another one of the highly effective methods listed above. The risk of venous thromboembolism continues for 4 to 6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone.

2.4 Dexamethasone – potential adverse events

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.

2. ^{18}F-FDG PET/CT

^{18}F-FDG PET/CT is a sensitive functional imaging modality. The updated International Myeloma Working Group (IMWG) criteria consider patients with focal skeletal lesions and increased uptake with underlying osteolytic destruction in one of the new imaging modalities as indicative of active myeloma (16, 17). In the last years, the significance of 18F-FDG PET and PET/CT in evaluation of MM has increased. PET/CT is considered a modality of high sensitivity in detecting both medullary and extramedullary disease, while its ability in treatment response assessment and its prognostic value have been documented (18-23). Although its routine application in the follow-up of MM is not yet recommended, ^{18}F-FDG PET/CT appears to be useful in the monitoring of MM and has been proposed to strengthen the evaluation of the quality of treatment response (17, 19, 20, 24-26).

3. RESEARCH HYPOTHESIS

KRd consolidation will demonstrate high efficacy in NDMM patients after standard first line treatment and can convert the patients that are PET-CT positive in to negativity. Elimination of PET-CT-positivity will be a supplement to elimination of MRD measured by Euroflow.

4. STUDY RATIONALE

PET-CT positivity after first line treatment is a prognostic marker for outcome. At ASH2015, Dr. Philippe Moreau presented data showing that PET-CT is an OS prognostic marker, that it is better than MRI, and that the best time to evaluate on this marker is pre-maintenance (Moreau et al, ASH 2015, Abstract 395). Between thirty and forty percent of the total of patients in these data were PET-positive after 8xRVD or 5xRVD+HDM-ASCT, although the complete data set is not yet available. This is probably marginally higher in the VTD/VCD+transplant population.. The following questions are as of today unanswered:

a) Can KRd consolidation eliminate PET-CT-positivity in these patients? In what proportion of patients?

b) How will elimination of PET-CT-positivity correspond to elimination of MRD measured by Euroflow?

In Europe, the most common induction regimes before autologous transplant is VTD and VCD. VRD will probably also be used increasingly in the coming years.. Even though other first-line regimes are in studies, financial matters will keep all mentioned regimes in use for an undetermined period, longer in some countries than in others. The choice of KRd is made on the basis that it will take time before K is a standard of care in first line, and even then, it will probably compete with other regimes. In the relative short term, most patients will not have received KRd in first line. Adding to that is the ASPIRE data where KRd is a standard-of-care treatment in next relapse.

There is an ongoing study of KRd vs R maintenance after ASCT (NCT02659293), where patients can be included disregarding their response status after transplant. In the present study proposal with a non-randomized study design, the focus is on the subgroup with PET-CT-positivity as this is increasingly being used as a measure of minimal residual disease complementary to phenotypic and molecular MRD assessment.

5. STUDY OBJECTIVES

6.1 Primary objective

To assess the proportion of patients that are PET-positive after standard first line treatment (transplant eligible patients), and how many of these can become PET-negative after four cycles of KRd consolidation.

6.2 Secondary objectives

The correspondence between PET-CT results and MRD dynamics by intra-patient comparison. Evaluating safety, quality of life and efficacy of KRd consolidation in this population.

6. 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), the Directive (2005/20/EG) and applicable regulatory requirements. The local investigator is responsible for the proper conduct of the study at the study site. National Ethic Committees and National Medicines Agencies in Norway,

Denmark and Sweden will approve the study protocol and any substantial amendment. 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 a statement of the reason to withdraw.

The clinical trial sponsor-investigator is the physical person or legal entity that is interested in the performance of the trial, signs requests for authorization addressed to the Regional Ethics Committee (REK) and regulatory authority of Norway and is responsible for the trial, including its performance, initiation and completion. The sponsor-investigator 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 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 national insurance systems for patients in clinical studies.

Each patient is assigned a unique patient study number at registration. In study documents, the patient´s identity is coded by a patient study number. The local investigator will keep a subject enrolment and identification log that contains the code key, 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, and only for monitoring visits, audits and inspections. The Information and Consent Form also explains that for data verification purposes, an authorized regulatory authority, an ethics review board or a monitor performing quality control

may require direct access to parts of the hospital or practice records relevant to the study including patients' medical history.

7.1 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 patient´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 patient´s willingness to continue participation in the study.

7.2 Patient confidentiality

Each patient is assigned a unique patient study number at registration. In study documents, the patient´s identity is coded by a 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 code key, 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, and only for 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.

7.3 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. 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.

7.4 Risk/benefit assessment

The patients eligible for this consolidation treatment are at higher risk of earlier relapse than average patients (see chapter 1.1), and positivity of PET-CT before maintenance treatment is the most important factor predicting overall survival. The selected patient group in this study is hence in need of better treatment and is a valid focus for a clinical study. Being in this situation, patients tend to desire more intensified therapy, and are in most cases willing to participate.

The KRd regime is proved safe and efficient for 18 consecutive cycles in relapsed patients (5), and has also recently demonstrated safety in extended treatment after transplant. As such, there is not expected to be any new safety issues with four cycles in this population. The relapse treatment has been with a lower carfilzomib dose of 27mg/m^2, because the population is more prone to adverse events. The KRd regime has also been tried in several smaller phase 1 and phase 1/2-studies in newly diagnosed multiple myeloma, both in young and elderly populations. In this situations 36mg/m^2 is a well-tolerated and effective regime, without new, unexpected or alarming safety problems.

However, intensified therapy will always come with a certain increase in adverse events. Patients will be informed about this. There are also practical strains with participating in studies, with more cumbersome examinations and for some patients a longer transport to the study center. The patients will also be informed about this, and that they can withdraw at any given time point.

Overall, the risk-benefit assessment for patients in this study looks acceptable.

7. INVESTIGATIONAL PLAN – STUDY DESIGN

This is an investigator initiated, academic, non-randomized, open-label multicenter study for consolidation in patients with multiple myeloma after standard first line treatment.

After a standard induction regime with ASCT, patients can be included in the study. A PET-CT will be performed, patients with a negative PET result will go out of the study, with a strong recommendation of standard-of-care treatment, as specified below. Patients with a positive PET result will receive four cycles of KRd followed by standard-of-care treatment with lenalidomide maintenance 10-15mg once daily

A new PET-CT-evaluation will be performed after completed consolidation. At inclusion in the study, MRD samples will be taken from all patients. We will repeat these samples after completed consolidation. The goals of the study are to evaluate what proportion of patients are PET-positive after standard first line treatment and how many of these can become PET-negative after KRd consolidation. The study will explore the dynamics of MRD status in this setting, and the correspondence between these two methods. Review of PET-CTs will be central and blinded.
The PET-CT-negative group will have long time follow up through their local doctor for PFS and OS
The study is a phase 2 study, with 50 PET-positive patients, to show the feasibility, safety and efficacy of this design.
Inclusion of patients will continue until 50 PET-positive patients have been included.

8. STUDY POPULATION

8.1 Inclusion criteria

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

1. At least 18 years of age, with at least 6 months expected survival.
2. Prior confirmed diagnosis of multiple myeloma (2014) (16).
3. Received standard first line treatment with at least a very good partial response (VGPR), according to IMWGs criteria . Standard first line treatment is defined as

VRD, VTD or VCD followed by ASCT with or without lenalidomide maintenance initiated (Patients where the monoclonal component or dFLC increases during the period from best response to screening can be included if there is no progressive disease.)

4. Patients must be carfilzomib naïve.
5. A positive PET-CT result from central reviewer in the screening period

6. Successful FISH evaluation performed with available results

7. 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.

8. Females of childbearing potential (FCBPs) must have a confirmed negative serum pregnancy test within the 7 days prior to inclusion

9. FCBPs and male subjects who are sexually active with FCBP must agree to use highly effective concomitant methods of contraceptive during the study and for 30 days following the last study drug dose. Male subjects must use contraception and refrain from donating sperm for at least 90 days after the last dose of carfilzomib.

10. Eastern Cooperative Oncology Group (ECOG) performance status 0-2. In patients >75 years of age, performance status 0-1.

11. Patients must meet the following adequate organ and bone marrow function within 21 days prior to inclusion:

    - Absolute neutrophil count (ANC) $\geq$ 0,5 x 10^9/L) and platelet count 35 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.

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

8.2 Exclusion criteria

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

1. Change of first line treatment because of stable or progressive disease.

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

3. Major surgery within 28 days before enrollment.

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

5. Patients who started treatment more than 12 month before screening

6. Central nervous system involvement.

7. Uncontrolled heart disease, including congestive heart failure (NYHA III-IV), uncontrolled angina pectoris, uncontrolled conduction abnormalities, acute diffuse infiltrative pulmonary disease, pericardial disease or myocardial infarction within 6 months prior to enrollment

8. Active hepatitis B or C 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. Another active malignancy. Patients with non-melanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.

13. Patients that have previously been treated with carfilzomib.

14. Primary plasma cell leukemia, systemic AL amyloidosis, Waldenströms macroglobulinemia, POEMS syndrome.

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

16. Ascites requiring ascites puncture within the 14 days prior to inclusion.

17. Previous allogeneic transplantation

18. Uncontrolled hypertension or uncontrolled diabetes despite medication

19. Contraindication to PET-CT

20. Not expected to tolerate full dose KRd

9. 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 a patient from the study for any of the following reason.

Adverse event

Protocol violation

Loss to follow-up

Progressive disease

Study termination

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

No compliance of the patient

Pregnancy

Death

Patients who are withdrawn from study will not be replaced. At the time of withdrawal, all study procedure outlines for the end of visit should be completed. The primary reason for patient´s withdrawal from the study should be recorded in the source documents and CRF. When the study is over or the patient withdraws for any reason, the patient will be treated according to standard-of-care in the Scandinavian countries.

10. END OF STUDY

Inclusion in the study ends when 50 patients have had positive initial PET-CT results. After progressive disease, patients will be followed by telephone for overall survival. Patients with negative PET-CT results will be followed by telephone/fax for progressive-free survival and overall survival every second month (±7 days).

The study will end with last patients last visit. There will be a post-study follow-up for overall survival in all patients, both with initial PET-CT positivity and negativity.

11.1 Stopping rules/discontinuation criteria/serious breach

The Investigator may discontinue the study for medical reasons, prior to inclusion of the intended number of patients. At the discretion of the Sponsor-investigator, the study may be discontinued for other reasons, prior to inclusion of the intended number of patients. A premature discontinuation of the study can be decided by the Sponsor in the following cases:

- The study is not conducted in accordance with the procedures defined in the approved protocol (i.e. protocol deviations, failure to ensure the quality of the data collected)
- If additional information which results in changes in the risk/benefit assessment becomes available
- The discovery of an unexpected and significant or unacceptable risk to the patients enrolled in the study.
- Failure of the Investigators to enter patients at an acceptable rate in the study as a whole

The Ethics Committee(s) and Regulatory Authorities will be informed by the sponsor about a premature discontinuation of the study. Reporting will be done in accordance with the required timelines.

11. TREATMENT

12.1 Study Drug Administration Schedule

28-day cycle

Cycles 1			
Agent	**Dose/day**	**Route**	**Days**
Carfilzomib	20 mg/m^2 36 mg/m^2	IV IV	1, 2 8, 9, 15, 16
Lenalidomide	25 mg	Oral	1-21
Dexamethasone	40 mg	Oral	1, 8, 15, 22

Cycles 2-4			
Agent	**Dose/day**	**Route**	**Days**
Carfilzomib	36 mg/m^2	IV	1, 2, 8, 9, 15, 16
Lenalidomide	25 mg	Oral	1-21
Dexamethasone	40 mg	Oral	1, 8, 15, 22

During Cycles 1-4, administration of carfilzomib can be adjusted within the following window:

Day 1 -0/+2 days

Day 2 ± 0

Day 8 -1/+1

Day 9 ± 0

Day 15 -1/+1

Day 16 ± 0

12.2 Carfilzomib administration

Patients will receive IV prehydration prior to the first 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 patient's condition and/or risk factors require hydration. 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 to protect from light until ready for reconstitution. Once carfilzomib is reconstituted and inspected, the clear solution may be stored between 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 body surface area (BSA) at baseline. Patients with a BSA > 2.2 m^2 will receive a dose based upon a BSA of 2.2 m^2. 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 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 glucose prior to and following carfilzomib infusion.

12.2.1 Dose modification guidelines for carfilzomib

In a case of study-related adverse event, the clinical investigator must assess its possible relationship to carfilzomib, lenalidomide and dexamethasone.

Local investigators can decide to not follow this dose modifications if they feel it is not in the best medical interest of the patient.

Carfilzomib dose reduction guidelines for toxicity and dose modification			
	1st dose reduction	2nd dose reduction	3rd dose reduction
36 mg/m^2	27 mg/m^2	20 mg/m^2	15 mg/m^2

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 this cycle is tolerated, the dose level prior to reduction may be resumed by the investigator´s discretion. If carfilzomib is stopped permanently due to toxicity, all study medication will be stopped and the patient will proceed to end-of-study visit.

12.2.2 Carfilzomib dosing guidelines for hematologic toxicity

Hematologic toxicity	**Recommended action**
Thrombocytopenia	
Platelets $\leq$ 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 $\geq$ 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.

12.2.3 Carfilzomib dosing guidelines for nonhematologic toxicity

Nonhematogical toxicity	Recommended action
Serum creatinine equal to or greater than 2 x baseline, or CrCl 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 withdrawn.

LVEF: For resting LVEF < 40% or reduction of LVEF to < 55% from baseline, if the drop is greater than 20% from 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.
PRES: posterior reversible encephalopathy syndrome; headache, altered mental status, seizures, visual loss, hypertension	Stop carfilzomib and study treatment and the patient is withdrawn from study. If visual or neurological symptoms, neuroradiological imaging is recommended.
Thrombotic microangiopathy (TMA)	If suspected, hold carfilzomib and manage per standard of care, including plasma exchange as clinically appropriate. If TMA is confirmed and related to carfilzomib, permanently discontinue carfilzomib. If the diagnosis is excluded, carfilzomib can be restarted
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

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.

12.3 Lenalidomide administration

Lenalidomide will be given on days 1-21 in 28-day-cycles. The dose will be 25mg unless reduced renal function (see 10.3.1). If the dose is missed, it should be taken as soon as possible within 12 hours. If over 12 hours have passed, the dose must be skipped. The subject should never take 2 doses at the same time.

12.3.1 Starting lenalidomide in renal failure

Category	Renal Function (Cockcroft-Gault)	Dose in MM
Moderate Renal Impairment	CLcr 30-50 mL/min	10 mg Every 24 hours
Severe Renal Impairment	CLcr < 30 mL/min (not requiring dialysis)	15 mg Every 48 hours
End Stage Renal Disease	CLcr < 30 mL/min (requiring dialysis)	5 mg Once daily. On dialysis days, administer the dose following dialysis.

If the dose is tolerated, it can be escalated according to local procedures.

12.3.2 Dose modification guidelines for lenalidomide

The dose modification guidelines as summarized below are recommended to manage both hematological and non-hematological toxicity. Local investigators can decide to not follow this dose modifications if they feel it is not in the best medical interest of the patient.

Hematological toxicity present at start of study should not lead to dose reduction.

Platelet counts	
Thrombocytopenia	
When Platelets	**Recommended Course**
Fall to <30,000/mcL	Interrupt lenalidomide treatment, follow CBC weekly
Return to ≥30,000/mcL	Resume lenalidomide at next lower dose. Do not dose below 2.5 mg daily
For each subsequent drop <30,000/mcL	Interrupt lenalidomide treatment
Return to ≥30,000/mcL	Resume lenalidomide at next lower dose. Do not dose below 2.5 mg daily
Absolute Neutrophil counts (ANC)	
Neutropenia	
When Neutrophils	**Recommended Course**
Fall to <1000/mcL	Interrupt lenalidomide treatment, follow CBC weekly
Return to ≥1,000/mcL and neutropenia is the only toxicity	Resume lenalidomide at 25 mg daily or initial starting dose
Return to ≥1,000/mcL and if other toxicity	Resume lenalidomide at next lower dose. Do not dose below 2.5 mg daily
For each subsequent drop <1,000/mcL	Interrupt lenalidomide treatment
Return to ≥1,000/mcL	Resume lenalidomide at next lower dose. Do not dose below 2.5 mg daily

12.4 Lenalidomide treatment after the four KRd cycles

Lenalidomide will be given according to the approved maintenance label for post-transplant patients, i.e. 10-15 mg daily continuously.

12.5 Dexamethasone administration

Dexamethasone will be given on days 1, 8, 15 and 22 in cycles of 28 days, and a dose of 40 mg PO. For subjects aged > 75 years, a daily low-dose dexamethasone dose of 20 mg is recommended.

For adverse events considered to be possibly due to dexamethasone treatment, the following dose reduction levels should be used:

Dose Level	Dexamethasone dose (PO)
0	40 mg
-1	20 mg
-2	12 mg
-3	0 mg

12.6 Concomitant treatment

A concomitant medication is defined as any prescription or over-the-counter preparation including vitamins. Concomitant medications received in conjunction with an AE/SAE will be described in the eCRF. Blood products must be reported on the appropriate eCRF.

12.6.1 Required concomitant medication

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

Antiviral

Valacyclovir 250-500 mg PO twice daily or an equivalent acyclovir is a required medication and should be continued for the duration of study treatment.

Thromboprophylaxis

There is an increased risk of thrombosis, predominantly deep venous thrombosis and pulmonary embolism (but also myocardial infarction and cerebrovascular events) in MM patients treated with lenalidomide and dexamethasone. The decision of antithrombotic prophylaxis (acetylsalicylic acid or LMWH) during maintenance treatment needs to be considered by individual risk assessment based on prior thrombosis history, smoking, hypertension, hyperlipidemia and paraprotein status. At least ASA 75 mg per day will be given as prophylaxis for all patients. Study patients should be closely monitored for symptoms of thrombosis.

Pregnancy and contraception

Highly effective contraception methods must continue throughout the study until 30 days after the last study drug administration, in FBCPs and men having sex with FCBPs. Estrogen-containing methods cannot be used, because of lenalidomides thrombogenic potential. The following methods are considered highly effective:

- Progestogen-only hormonal contraception associated with inhibition of ovulation
- Injectable
- Implantable
- Intrauterine device
- Intrauterine hormone-releasing system (not containing estrogen)

- Bilateral tubal occlusion
- Vasectomized partner
- Complete sexual abstinence

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.

12.6.2 Optional and allowed concomitant medication

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 they are not to be given 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.

12.6.3 Prohibited and/or restricted treatments

Other anti-myeloma treatment than study protocol treatment during the study is not allowed. Glucocorticoids are allowed for nonmalignant situation like asthma with a dose of no more than ≤ 4 mg/day dexamethasone or prednisone ≤ 20 mg/day.

12.7 Study drug assignment

This is an open-label study without any randomization or stratification. All patients will use the same study treatment protocol.

12.8 Study drug packaging, 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 document a drug medication diary during protocol treatment, including dose, batch number, shelf life and amount.

Lenalidomide

Lenalidomide 25mg will be taken orally with the morning breakfast. Study sites will document a drug medication diary during protocol treatment, including dose, batchnr, shelf life and amount. This drug will be reimbursed as routine medication, with labelling written locally by the treating physician in the study:

Dexamethasone

Dexamethasone 40 or 20 mg will be taken orally with the morning breakfast. Study sites will document a drug medication diary during protocol treatment, including dose, batch number, shelf life and amount. This drug will be reimbursed as routine medication, with labelling written locally by the treating physician in the study.

12.9 Study compliance

Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified sub-investigator(s). The appropriate study personnel will maintain records of study drug receipt and dispensing. The personnel will maintain accountability records of study drug, including information such as study drug name, dose/strength, batch number, date and no. of capsules dispensed, date and no. of capsules returned and finally date destroyed.

12. STUDY ASSESSMENTS AND PROCEDURES

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

13.1 Medical previous history

- complete medical history
- present symptoms
- history of thrombosis of the patient
- history of any other malignancies of the patient
- performance status (ECOG)
- recent infections

- bone symptoms
- bleeding
- polyneuropathy
- gastrointestinal symptoms

13.2 Physical examinations

- standard physical examination with cardiovascular and targeted neurological (polyneuropathy, autonomic neuropathy) examinations
- blood pressure
- body weight and height, surface area
- investigation for infections and bleedings

13.3 Hematology

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

13.4 Blood chemistry

Blood, bone marrow and urine samples will be sampled according to the flow chart.

13.5 Immunochemistry

Serum protein electrophoresis and immunofixation (IFE) at study entry, start of every cycle and every two months until progression. 24-h urine electrophoresis and immunofixation at study entry, the start of every cycle and every two months until progression. Serum free light chains (S-FLC) at study entry, start of every cycle and at every two months until progression

13.6 Bone marrow assessment

Bone marrow sample will be collected at entry for multiparameter flow cytometry (MFC), and one month after Cycle 4 day 28.It is important to collect the first pull and no more than 2 mL to avoid haemodilution, where after the aspiration is put intoan EDTA tube. Bone marrow aspirate and biopsy will be collected and analyzed one month after Cycle 4 day 29 and every time CR/sCR are suspected.

13.7 Specific additional investigations

- Bone imaging: PET-CT at screening. Patients with avid lesions will receive the protocol treatment. A subsequent PET-CT will be performed at Visit D1.
- Electrocardiogram from all patients at entry, and if clinically indicated
- MRD analysis by Euroflow at entry and at visit after C4D29.
- Patient reported QOL forms (The European Organisation for Research and Treatment of Cancer Quality of life questionnaire (EORTC QLQ-C30) + question of shortness of breath filled in at screening, before each cycle of KRD, at day 15 of each KRD cycle, at one and three months after end of KRd, and at end of treatment (Progressive disease). The EORTC QLQ-CIPN20 questionnaire evaluating peripheral neuropathy will be filled in at C1D1 and Visit D1.
- Pregnancy tests will be performed monthly from study start until 4 weeks after end of treatment with carfilzomib/lenalidomide.

13. SAFETY

Study investigators must follow the study protocol treatment and follow the dose reduction and adjustment guidelines in every study patient. Dose interruptions and modifications from other reasons can be performed at physician's discretion. Exceptional issues should be discussed with the principal investigator. Adverse event will be documented if observed, mentioned during open questioning, or when spontaneously reported.

14.1 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 to AMGEN. AEs occurring in the same period will be registered.

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.

14.2 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).

14.3 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 (e.g., 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.

Suspected transmission of an infectious agent (e.g., 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 (e.g., 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 (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)

14.3.1 Serious Adverse Event Collecting and Reporting

If any SAE occurs during the study it need to be reported on the SAE form in the web-CRF. For each SAE, the investigator will provide the following information: type of event, date initiated/observed, severity, action taken, outcome and possible relation to study medication. The forms will be provided to and be kept by the

sponsor. SAE forms will be available to the independent monitor. All SAEs should be reported to the sponsor-investigator within 24 hours after the investigator has been aware of the SAE. The investigator should take all appropriate measures to ensure the safety of the patients. He or she should follow up the outcome of SAE until resolution of the patient's condition

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 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.

SAEs, whether related or unrelated to the study drug, and pregnancies, must be reported to AMGEN within 24 hours. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form. The study secretariat in Oslo will report to Amgen. If an SAE is clearly related to the progression of myeloma, the SAE should not be reported.

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 additional information becomes available, a follow-up SAE report should be sent within 24 hours to the sponsor-investigator using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

14.4 Health Authority Reporting (SUSAR reporting)

14.4.1 Definition of SUSAR

SUSAR is defined as a suspected unexpected severe adverse event that is not listed in the IB for carfilzomib, and in the SPC for lenalidomide and dexamethasone.

14.4.2 Reporting of SUSAR

The sponsor-investigator is responsible for informing the regulatory authorities, the European Medicines Agency and the ethics committees of any individual case report of SAEs that are determined to be a SUSAR. The Investigator will ensure all relevant information is provided to the sponsor-investigator to allow the sponsor-investigator to meet their obligations to report the SUSAR.

Any life-threatening SUSAR will be reported by the sponsor as soon as possible (and not later than 7 days after the sponsor-investigator has become aware of the occurrence and with an up-date with relevant information within an additional 8 days). Any other SUSAR will be reported as soon as possible or within 15 days after the sponsor-investigator has become aware of it. The SUSARs will be reported to companies with SAE report form and to the Medical Agencies in the different countries.

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 Sponsor-investigator shall notify the health authority by e-mail on a CIOMS form, 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. SAE´s will be reported 60 days after last study drug dose but SUSAR´s will be reported 1 year after last study drug dose.

14.5 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. The following non-serious adverse events will not be reported:

- A pre-existing condition that does not increase in severity; the pre-existing condition should be reported on the baseline concomitant diseases CRF
- AE’s of CTCAE grade 1

- Abnormal laboratory values that have been recorded as being not clinically significant by the investigator in the source documents

- Nausea/vomiting

- Progression of the disease under study; complaints and complications as a result of disease progression

14.5.1 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.

14.6 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 (e.g., dose tapering if necessary for subject safety).
The investigator must immediately notify AMGEN and the sponsor-investigator 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 to AMGEN. 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 (e.g., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

14.7 Overdose

Definition of overdose in this study is any accidental dose higher than specified in the protocol. 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.

14.9 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 non-serious or serious adverse event, as appropriate, and reported accordingly.

14. DATA MONITORING

The monitoring of the study will be organized and led by Fredrik Schjesvold after agreement with the Steering Group of the study. In Sweden and Norway, independent monitors from Clinical Studies Sweden – Forum South at Skåne University Hospital will perform the monitoring. A monitoring plan describing the monitoring activities will be developed. In Denmark, monitors from the two GCP units (in Copenhagen and Odense) will carry out the monitoring.

Monitoring will be performed before, during and after the study, according to ICH-GCP guidelines, with emphasis on legal and safety data, plus endpoint and response evaluation.

Each main study center will be visited before starting the first patient; this prestudy visit will include information on the study, identification of the local study team, and

control of their knowledge of the GCP rules and the protocol regulations. Necessary documents in the investigator study file will be identified and controlled. The local handling of the study drug will also be controlled, with the study staff and the hospital pharmacy.

During the study, each center will be visited after inclusion of the first 1-2 patients and thereafter once or twice yearly. The local investigator will give the monitor direct access to the patients' hospital files, original laboratory data and Case Report Forms. At these visits, the monitor will control that the included patients' consent forms are obtained in correct time, and documented in the hospital files; that patients are included in accordance with the protocol; that adverse events are correctly documented and reported; that the data necessary for evaluation of response and relapse are collected and documented; and that the study drug handling is performed correctly.

After study termination, a final visit to each center will be performed to control that all data are correctly collected, that the CRFs are complete and reported to the study secretariat. The monitor will assist the local study investigator in preserving the study material according to GCP rules.

15.1 Handling of documents and data

All sites will enter data in a web-based electronic CRF, and the local investigator or study nurse can sign the CRF. There will be back-up of data at the data centre in Oslo, and all people working on the files will need login details from the sponsor-investigator. Documents that are essential for evaluation of study conduct and data quality 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.

15.2 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 sponsor-investigator. Substantial 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 Ethics Committee and the regulatory authorities.

The sponsor-investigator will make an annual safety report that will be sent to the ethical committees and regulatory authorities, where the safety of the study will be judged and evaluated. A list of SAEs and SUSARs will be included.

15.3 Quality-of-Life

The Quality of life data will be handled by Quality of Life Research Centre, Odense (QoLRC-OUH) and will be stored in the Electronic data capture platform, REDCap database. The quality of life data collection of the protocol will be approved by Odense Patient Explorative Data Network (OPEN), University of Southern Denmark, Denmark, who has a license to the REDCap database. A Data Processing agreement will be obtained between the approval Data Protective Agency in Norway and OPEN and an OPEN license agreement will be obtained between OPEN and QoLRC-OUH as a representative for the sponsor and the sponsor.

15. STATISTICAL CONSIDERATIONS

16.1 Sample size determination

The objective of the study is to describe the proportion of patients still PET-positive after standard first line treatment in the Nordics, and to describe how many of these can become PET-negative after consolidation with KRd. The study is a phase 2 study looking at the feasibility and safety of this approach. Fifty PET-positive patients is considered acceptable to achieve this objective, see Table below for precision of the estimates with different proportions. We anticipate a 50% PET- CT-positivity after first line treatment in the total population, which amounts to 100 pts screened with PET-CT initially. 50 PET-CT+ patients will be included.

Proportion	Confidence Interval
0.1	(0.043 - 0.214)
0.2	(0.112 - 0.330)
0.3	(0.191 - 0.438)
0.4	(0.276 - 0.538)
0.5	(0.366 - 0.634)
0.6	(0.462 - 0.724)
0.7	(0.562 - 0.809)
0.8	(0.670 - 0.888)
0.9	(0.786 - 0.957)

16.2 Endpoint definitions

Primary endpoint:

- Change from PET-CT positivity to PET-CT negativity at visit D Proportion of PET-CT positivity after standard first line therapy

Secondary endpoints are

- Change from MRD positivity to MRD negativity at visit D, as assessed by 8-colour Euroflow multiparameter flow cytometry
- Overall response after each treatment cycle.
- Progression-free survival (PFS) as defined as time from treatment initiation to progression defined using IMWG criteria for progressive disease.
- Time to next treatment (TTNT) as defined as time from treatment initiation (start of cycle 1) to start of cycle 1 in next cancer treatment cycle.
- Overall survival (OS) as defined as time from treatment initiation (start of cycle 1) to time of death
- Quality-of-Life (section 15.3 and study flow chart)

16.3 Population for Analysis

The following populations will be considered for the analysis:

- The modified intention to treat (mITT) population is defined as all included patients with at least a single dose of study drug.
- The per-protocol population (PP) will include patients in the mITT population who sufficiently comply with the protocol. Criteria for inclusion in the PP population will be defined prior to database lock.

- The safety population will include all patients with at least a single dose of study drug, identical to the mITT population.

16.4 Planned analyses

The main statistical analysis is planned when

- The planned number of patients have been included
- All included patients have either finalised their last assessment of the primary endpoint or has/is withdrawn according to protocol procedures
- All data have been entered, verified and validated.

Further analyses will be performed subsequently to the main analyses as more efficacy data are available (such as disease progression and death).

16.5 Statistical analyses

The primary parameter to be estimated is the proportion of patients with a negative PET-CT with 95% confidence limits by the Wilson method. The primary analysis will be performed on the mITT population.

Dichotomous endpoints will be handled as the primary parameter in addition to mixed model logistic regression for repeated measurements. Time to event endpoints will be presented using Kaplan-Meier plots, while repeated continuous endpoints will be analysed using linear mixed models. All parameters will be analysed both in the mITT and PP populations.

Unless otherwise specified, all estimates will be presented with 95% confidence limits. Parameter estimates might be compared to historical estimates, pre-specified prior to any analyses.

16.6 Safety analyses

Safety analyses will be performed in the safety population. Safety analyses will be descriptive and presented as summary tables.

16.7 Missing data

For dichotomous endpoints, missing data will be handled using worst case imputation. No imputation will be performed for time-to-event data, and incomplete registrations of event will be censored at last time of contact. Continuous endpoints will be analysed using mixed modes giving unbiased estimates under the assumption of missing at random.

Robustness analyses including complete case analyses, last observation carried forward, best case imputation and multiple imputation techniques might be considered if the rate of missing data is substantial.

16.8 Demographic and baseline characteristics

Baseline characteristics will include the 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, ionized calcium, liver enzymes, LD, bone marrow plasma cell count, bone marrow multiparameter flow cytometry. Bone imaging will include PET-CT

16.STUDY MANAGEMENT

17.1 Compliance with the protocol

Principal investigators of each study site are responsible to follow the protocol and inform the sponsor-investigator of the whole study immediately of any possible protocol violations, any severe adverse events and any suspected unexpected serious adverse reactions (SUSAR´s). Principal investigator must confirm that any protocol revisions or amendments will be noticed and followed in each study site. All potential serious breaches must be reported to the regulatory authorities immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the patients of the study or the scientific value of the study.

17.2 Publication

The results of this study will be written for publication by the sponsor-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. AMGEN will have the possibility to review the publication three weeks before submission but the publication is owned and written by academic investigators.

At least one of the authors from Region of Southern Denmark and/or University of Southern Denmark will have Odense Patient data Explorative Network (OPEN) as affiliation, as described in the OPEN license agreement.

17.3 Destruction of investigational products

After completion of study, each study site will destroy the study drugs by detailed guidelines of destruction and all procedures will be documented by the pharmacy of the study site.

17.4 Significant changes of the protocol

The sponsor is responsible to report any significant changes of the protocol made during the study to the Ethics Committee and the Swedish Medical Products Agency and ask for their approval.

Significant changes are defined as:

1) change of treatment duration or dosage of any of the study medications

2) change of study endpoints

3) change of methods of evaluation of response

4) change of inclusion or exclusion criteria, withdrawal criteria and sponsor's criteria for premature termination of the study

The patient information will be updated and the included patients will be informed regarding the change and will have the opportunity to re-signed the up-dated version of the patient information.

The patient information will also be up-dated if new and/or essential information affecting the trial will arise and the patients will have the opportunity to re-sign the revised patient information.

17. USER PARTICIPATION: Letter from Blodkreftforeningen

BLODKREFT FORENINGEN
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Telefon 97 62 75 11
www.blodkreftforeningen.no

Oslo, 25th of April 2017

User-participation in the phase II CONPET-study

The user group in this study has been defined as patients with multiple myeloma, and their next of kin. Blodkreftforeningen (The Norwegian Blood Cancer Association) has been asked to participate in this study on behalf of the user group.

This letter is to confirm that Blodkreftforeningen is informed about the planned clinical study entitled "*KRd consolidation in myeloma patients with a positive PET-CT after standard first line treatment. A phase II study*, and we have had the opportunity to comment on a preliminary version of the Study Protocol. We are also informed about a project application regarding this study entitled "*PET/CT positivity as a predictor for KRd consolidation treatment of myeloma patients; The CONPET study*".

We have reviewed the project and understand that this is a clinical study with new treatment for a high-risk patient population, as well as a study with several other beneficial aspects, as exploring PET-CT assessment and establishing MRD Euroflow in Norway.

We are supportive to the project as we see both immediate and future benefit for Norwegian patients. We consider a study in this field led from Norway (which is a novelty) to be of importance for competence building. We have been asked to participate in the development, implementation, (dissemination) and utilization of the project results and are prepared to contribute in this respect.

Specifically, we will give feedback on the protocol before this is completed. Regarding dissemination of results, we will consider using our web as well as our annual patient seminars.

Best regards

Blodkreftforeningen

Eddy Grønset — Head of secretary

Jacob Hygen — Vice president (sign)

18.APPENDICES

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 (e.g., 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

APPENDIX 2. NYHA Classification

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 3. International staging system (ISS)

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 4. International Myeloma Working Group uniform response criteria by response subcategory for multiple myeloma (additional details are available in the paper (3)

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 disease

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 any time 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.

APPENDIX 5. Diagnostic criteria.

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 A
  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

  Biomarkers
  1. Ratio of involved/uninvolved light chain >100
  2. Bone marrow plasma cells > 60%
  3. More than 1 MR lesion > 5mm

APPENDIX 6. PET-CT protocol

The PET-CT protocol exists as a separate document

References

1. Liwing J, Uttervall K, Lund J, Aldrin A, Blimark C, Carlson K, et al. Improved survival in myeloma patients: starting to close in on the gap between elderly patients and a matched normal population. Br J Haematol. 2014;164(5):684-93.
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