The Rogosin Institute

INVESTIGATOR INITIATED STUDY PROTOCOL

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Protocol Number:
X05320

Protocol Title:
VELCADE® Therapy for Severe IgA Nephropathy

Protocol Version:
1.6

Date of Protocol:
11/28/11

*VELCADE is the exclusive trademark of Millennium Pharmaceuticals, Inc., registered in the United States and internationally.

INVESTIGATOR SIGNATURE PAGE

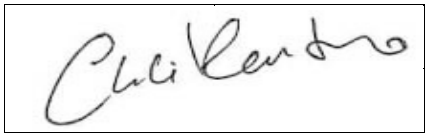
INVESTIGATOR STATEMENT

I have read the protocol, including all appendices and in its latest version. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

As the principal investigator, I will conduct the trial in accordance with the guidelines of Good Clinical Practice (GCP), including the archiving of essential documents, the Declaration of Helsinki, any applicable local health authority requirements, and Institutional Review Board (IRB) requirements.

Choli Hartono, MD

Principal Investigator Name (Printed)



Principal Investigator Signature

The Rogosin Institute	**11/28/11**
Institution	**Signature Date**

PROTOCOL SUMMARY

Title: VELCADE® Therapy for Severe IgA Nephropathy

Objectives
The primary objective of this study is to investigate the safety and ability of VELCADE to induce complete or partial remission in subjects with severe IgA nephropathy and risk factors for progression of disease.

The secondary objectives of this study are to assess clinical outcomes relating to safety and efficacy, such as infection, malignancy, preservation of renal function, partial responders, relapse rate, and reduction in the requirement of anti-hypertensive drugs; and to study mechanistic assays to predict remission.

Subject population
Each subject must meet all of the following **inclusion** criteria to be enrolled in the study:

1. Male or female, 18 years of age or older.
2. Subject is capable of understanding the purposes and risks of the study, is willing to participate in and comply with the study, and can give voluntary written informed consent before performance of any study-related procedure not part of normal medical care, with the understanding that consent may be withdrawn by the subject at any time without prejudice to future medical care.
3. Female subject is either post-menopausal or surgically sterilized or willing to use an acceptable method of birth control (i.e., a hormonal contraceptive, intra-uterine device, diaphragm with spermicide, condom with spermicide, or abstinence) for the duration of the study.
4. Male subject agrees to use an acceptable method for contraception for the duration of the study.
5. Subjects must have biopsy proven severe IgA nephropathy.
6. Within 14 days before enrollment, creatinine clearance as measured by MDRD formula must be greater or equal to 30 cc/min/1.73 m^2.
7. Prior to enrollment, quantified proteinuria (via 24 hr urine collection or spot urine protein and creatinine ratio) must be greater or equal to 1000 mg.
8. Unless contraindicated subject must be on stable doses of ACEI and/or ARB and/or renin inhibitor for at least 4 weeks prior to screening.

Subjects meeting any of the following **exclusion** criteria will not be enrolled in the study:

1. Subject has a platelet count of less than 30×10^9/L within 14 days before enrollment.
2. Subject has an absolute neutrophil count of less than 1.0×10^9/L within 14 days before enrollment.
3. Subject has ≥Grade 2 peripheral neuropathy within 14 days before enrollment.
4. Myocardial infarction within 6 months prior to enrollment or has New York Heart Association (NYHA) Class III or IV heart failure (see section 8.3), uncontrolled angina,

severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities. Prior to study entry, any ECG abnormality at screening has to be documented by the investigator as not medically relevant.

5. Subject has hypersensitivity to VELCADE, boron or mannitol.
6. Female subject is pregnant or breast-feeding. Confirmation that the subject is not pregnant must be established by a negative serum β-human chorionic gonadotropin (β-hCG) pregnancy test result obtained during screening. Pregnancy testing is not required for post-menopausal or surgically sterilized women.
7. Subject has received other investigational drugs within 14 days before enrollment.
8. Serious medical conditions and infections (including HIV, HCV, HBV) or psychiatric illness likely to interfere with participation in this clinical study, as determined by review of the medical history.
9. Diagnosed or treated for another malignancy within 3 years of enrollment, with the exception of complete resection of basal cell carcinoma or squamous cell carcinoma of the skin, an in situ malignancy, or low-risk prostate cancer after curative therapy.
10. Subject has total bilirubin greater than 1.5 x upper limit of normal.

Number of subjects
10 adult subjects with IgA nephropathy.

Study design and methodology
This exploratory single center, open-label, single treatment group assignment, safety and efficacy study will enroll 10 subjects with severe IgA nephropathy. Subjects will receive 4 doses of VELCADE (1 cycle) to induce clinical remission. Non-responders after a 4-week observation period will receive a second successive cycle of VELCADE.

Treatments administered
Subjects will receive 4 doses of VELCADE at 1.3 mg/m^2 on days 1, 4, 8, and 11 (1 cycle). Non-responders will receive a second cycle at similar dosages. Subjects will receive acyclovir prophylaxis.

Efficacy data collected
The following evaluations will be conducted to assess the efficacy of VELCADE:

1) Quantification of urinary protein.
2) Blood pressure monitoring.
3) Measurement of serum creatinine.
4) Urinalysis.

Safety data collected
The following evaluations will be conducted to assess the safety of VELCADE:

1) Monitoring of CBC.
2) Clinical follow-up for infections and malignancy.

Statistical procedures
For this pilot study, proportion of subjects with clinical remission or partial response will be analyzed.

TABLE OF CONTENTS

ABBREVIATIONS LIST

Abbreviation	Definition
°C	degrees Celsius
μM	micromolar
20S	20S proteasome subunit
ACEI	angiotensin converting enzyme inhibitor
AE	adverse event
ANC	absolute neutrophil count
ARB	angiotensin receptor blockade
Bc1-2	B-cell lymphoma-2; a gene that inhibits apoptosis
BSA	body surface area
CAM	cell adhesion molecules
cm	centimeter
CR	Complete Response
CTCAE	(NCI) Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CV	cardiovascular
dL	deciliter
DLT	Dose Limiting Toxicity
DNA	deoxyribonucleic acid
FDA	Food and Drug Administration
EBMT	European Group for Blood and Marrow Transplant
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GI	gastrointestinal
ht	height
IκB	I kappa B kinase; cytokine response kinase that activates transcription factor NF-kappa b at serine 32 and 36
ICAM-1	intercellular adhesion molecule 1
ICH	International Conference on Harmonisation
IL-6	Interleukin-6
iPs	immunoproteasomes

Abbreviation	Definition
IND	Investigational New Drug
IRB	Institutional Review Board
IV	intravenous
IκBα	I kappa B alpha-associated protein kinase
kg	kilogram
Ki	inhibitory constant
lbs	pounds
m^2	square meters
mg	milligram
min	minute
mL	milliliter
mm^3	cubic millimeters
mmol	millimole
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NF-κB	nuclear factor-κB
ng	nanogram
nM	nanomole
p21	p21(ras) farnesyl-protein transferase
p27	cyclin-dependent kinase inhibitor
p53	tumor suppressor protein with molecular weight of 53 kDa
PBMC	peripheral blood mononuclear cell
pIgA1	polymeric immunoglobulin A1
PK	pharmacokinetics
SAE	serious adverse event
US	United States
USP	United States Pharmacopeia
VCAM-1	vascular cell adhesion molecule 1
w/w	weight-to-weight ratio
wt	weight

1 INTRODUCTION AND STUDY RATIONALE

1.1 Overview of the Disease

IgA nephropathy is the most common glomerular disease in the world. Retrospective studies of affected patients reveal that the prognosis is highly variable with actuarial renal survival at 10 years varying from 57% to 85% (D'Amico 2000). The natural history of the disease is not benign with 60% of patients developing advance chronic or end-stage renal disease by 20 years (Samuels et al., 2004).

There is no good animal model for IgA nephropathy. In the 40 years since it was first characterized (Berger et al., 1968), understanding the pathogenesis and causation has been a challenging process. Studies to date suggest that the pathogenesis is the deposition of abnormal polymeric IgA1 (pIgA1) immunoglobulins in the mesangium of kidney glomeruli causing an inflammatory immune response. Pathogenic pIgA1s in patients with IgA nephropathy have abnormal O-galactosylation at the hinge region. The aberrant pIgA1s have a propensity to form immune complexes and accumulate in the kidney mesangium. There is evidence of increased plasma cells secreting altered pIgA1 in the bone marrow and tonsils of subjects with IgA nephropathy (Barratt et al., 2005). Serum IgA level is elevated in up to 50% of patients at some point in the course of the disease.

Transcription factor nuclear factor-κB (NF-κB) mediates the inflammatory immune response (cytokines, growth factors, and adhesion molecules) to abnormal pIgA1 deposition in the kidney mesangium. Expression of NF-κB in kidney glomeruli and the interstitium correlated with progressive kidney tissue injury (Ashizawa et al., 2003).

In vitro production of IL-6 by kidney mesangial and tubular cells can be stimulated by exposure to serum of subjects with IgA nephropathy (Wada et al., 2003). Urinary IL-6 levels in subjects with progressive disease were significantly higher than stable subjects suggesting that elevated urinary IL-6 levels could be used to prognosticate disease (Harada et al., 2002).

A switch to immunoproteasomes (iPS) was detected in peripheral blood mononuclear cells (PBMCs) of patients with IgA nephropathy and significant proteinuria. Specifically, the switch to iPS of the chymotrypsin-like catalytic subunits (LMP7/β5) was significantly higher in IgA subjects not in clinical remission (Coppo et al., 2009).

The risk for progression to end-stage renal disease is highest in patients with the following risk factors: elevated serum creatinine at presentation, significant proteinuria (greater than 1gm/day), hypertension, and persistent microhematuria (Goto et al., 2009; Mackinnon et al., 2008; Reich et al., 2007). An international consensus report also proposed pathological features (mesangial hypercellularity, tubular atrophy/interstitial fibrosis, segmental glomerulosclerosis) that could prognosticate renal survival (Cattran et al., 2009).

Optimal therapy for the high-risk group to slow the deterioration of kidney function is ill defined. The pathogenesis of the disease has to be further investigated but initial events eliciting abnormal pIgA1 deposition in the kidney lead to an inflammatory response, which provides a rationale for immunomodulatory therapy (Floege et al., 2008). Immunosuppressive medications such as azathioprine, corticosteroids, cyclophosphamide, and mycophenolate mofetil have been investigated as possible treatment for aggressive IgA kidney disease. A clinical trial is ongoing for a B cell modulating drug (anti-CD20 monoclonal antibody) as a possible therapeutic agent for high-risk individuals. There is no consensus on the use of immunomodulatory agents for severe IgA nephropathy. Corticosteroid therapy had the most promise in a meta-analysis of randomized controlled trials (Samuels et al., 2004). However, prolonged corticosteroid therapy has serious side effects including osteoporosis, hyperglycemia, significant weight gain, hypertension, and major infections.

In this pilot study, we aim to investigate the effect of VELCADE in subjects with severe IgA nephropathy. VELCADE is a proteasome inhibitor and potentially has activity against non-cancerous plasma cells (Perry et al., 2008). VELCADE may abrogate the production of abnormal pIgA1 in IgA nephropathy. VELCADE may mitigate the expression of NF-κB in the kidney and reduce the inflammatory response to abnormal pIgA1 deposition. Finally, VELCADE may interfere with the upregulation of iPS and promote clinical remission in severe IgA nephropathy.

1.2 VELCADE for Injection

1.2.1 Scientific Background

VELCADE for injection is a small molecule proteasome inhibitor developed by Millennium Pharmaceuticals, Inc., (Millennium) as a novel agent to treat human malignancies. VELCADE is currently approved by the United States Food and Drug Administration (US FDA) and it is registered in Europe for the treatment of multiple myeloma patients who have received at least one prior therapy.

By inhibiting a single molecular target, the proteasome, VELCADE affects multiple signaling pathways. The anti-neoplastic effect of VELCADE likely involves several distinct mechanisms, including inhibition of cell growth and survival pathways, induction of apoptosis, and inhibition of expression of genes that control cellular adhesion, migration and angiogenesis. Thus, the mechanisms by which VELCADE elicits its antitumor activity may vary among tumor types, and the extent to which each affected pathway is critical to the inhibition of tumor growth could also differ. VELCADE has a novel pattern of cytotoxicity in National Cancer Institute (NCI) in vitro and in vivo assays (Adams et al., 1999). In addition, VELCADE has cytotoxic activity in a variety of xenograft tumor models, both as a single agent and in combination with chemotherapy and radiation (Steiner et al., 2001; Teicher et al., 1999; Cusack et al., 2001; LeBlanc et al., 2002; Pink et al., 2002). Notably, VELCADE induces apoptosis in cells that over express bcl-2, a

genetic trait that confers unregulated growth and resistance to conventional chemotherapeutics (McConkey et al., 1999).

VELCADE is thought to be efficacious in multiple myeloma via its inhibition of nuclear factor κB (NF-κB) activation, its attenuation of interleukin-6 (IL-6)-mediated cell growth, a direct apoptotic effect, and possibly anti-angiogenic and other effects (Hideshima et al., 2001).

1.2.2 Nonclinical Pharmacology

Pharmacokinetic (PK) and pharmacodynamic studies were conducted in the rat and cynomolgus monkey. Upon intravenous (IV) bolus administration, VELCADE displays a rapid distribution phase ($t_{1/2}\alpha$ <10 minutes) followed by a longer elimination phase ($t_{1/2}\beta$ 5–15 hours). VELCADE has a large volume of distribution (range 5–50 L/kg). The plasma PK profile is well described by a 2-compartment model.

The pharmacodynamic action of VELCADE is well established and can be measured through an ex vivo assay (20S proteasome activity) (Lightcap et al., 2000). This assay was used to determine the duration of drug effect in lieu of the PK data in the early preclinical toxicology studies as well as to set a guide for dose escalation in humans. Following dosing with VELCADE in the rat and cynomolgus monkey, proteasome inhibition in peripheral blood had a half-life less than 24 hours, with proteasome activity returning to pretreatment baseline within 24 hours in monkey and within 48 to 72 hours in rat after a single dose of VELCADE. Further, intermittent but high inhibition (>70%) of proteasome activity was better tolerated than sustained inhibition. Thus, a twice-weekly clinical dosing regimen was chosen in order to allow return of proteasome activity towards baseline between dose administrations.

1.2.3 Nonclinical Toxicity

Single-dose IV toxicity studies were conducted with VELCADE in the mouse, rat, dog, and monkey to establish the single-dose maximum tolerated dose (MTD). The MTDs were 0.25 mg/kg (1.5 mg/m^2) and 0.067 mg/kg (0.8 mg/m^2) in the 2 most sensitive species, rat and monkey, respectively.

Repeat-dose multi-cycle toxicity studies of 3 and 6 months in the rat and 9 months in the monkey, each with 8-week recovery periods, were conducted to characterize the chronic toxicity of VELCADE when administered by the clinical route and regimen of administration. The MTD in the 6-month rat study was 0.10 mg/kg (0.6 mg/m^2) and the key target organs were the gastrointestinal (GI) tract, hematopoietic and lymphoid systems. The MTD in the 9-month monkey study was 0.05 mg/kg (0.6 mg/m^2) and the key target organs were the GI tract, hematopoietic and lymphoid systems, peripheral nervous system, and kidney. Full or partial reversibility was observed for each of the toxicities described to date.

In general, the nature of the toxicity of VELCADE is similar across species, and target organs of toxicity in animals have been largely predictive of human toxicity. The toxicity of VELCADE in animals is characterized by a steep dose-response with mortality seen at dosages above the MTD.

The cause of death at acutely lethal dosages is considered to be related to indirect cardiovascular (CV) effects of hypotension and vascular changes with secondary bradycardia and the cause of death in long-term studies has been attributed to GI or hematologic toxicity. The pharmacologic effects of VELCADE on the CV system have been extensively characterized and have demonstrated that indirect effects on CV function occur only at acutely lethal dosages and are abrogated by routine supportive care.

Additional detailed information regarding the nonclinical pharmacology and toxicology of VELCADE may be found in the Investigator's Brochure.

1.2.4 Clinical Pharmacokinetics and Pharmacodynamics

The clinical pharmacology characterization of VELCADE has been determined from phase 1 studies in subjects with solid tumors and hematological malignancies, and confirmed in phase 2 studies in subjects with multiple myeloma.

VELCADE demonstrates multi-compartmental pharmacokinetics. Following intravenous administration of 1.0 mg/m^2 and 1.3 mg/m^2 dose, the mean first-dose maximum observed plasma concentrations of VELCADE were 57 and 112 ng/mL, respectively in 11 subjects with multiple myeloma and creatinine clearance values >50 mL/min participating in a pharmacokinetics study. In subsequent doses, mean maximum observed plasma concentrations ranged from 67 to 106 ng/mL for the 1.0 mg/m^2 dose and 89 to 120 ng/mL for the 1.3 mg/m^2 dose. The mean elimination half-life of VELCADE upon multiple dosing ranged from 40 to 193 hours.

VELCADE is eliminated more rapidly following the first dose. Mean Total Body Clearances were 102 and 112 L/h following the first dose for doses of 1.0 mg/m^2 and 1.3 mg/m^2, respectively, and ranged from 15 to 32 L/h following subsequent doses for doses of 1.0 and 1.3 mg/m^2, respectively. Clinical experience has shown that the change in clearance does not result in overt toxicity from accumulation in this multidose regimen in humans.

In subjects with advanced malignancies, the maximum pharmacodynamic effect (inhibition of 20S activity) occurred within 1-hour post dose. At the therapeutic dose of 1.3 mg/m^2 in subjects with multiple myeloma, the mean proteasome inhibition at 1-hour post dose was approximately 61%.

The time course of proteasome inhibition in subjects is characterized by maximum inhibition observed within the first hour after administration, followed by partial recovery of proteasome activity over the next 6 to 24 hours to within 50% of the pretreatment activity. On the Day 1, 4, 8, and 11 schedule, variable (10%–30%) levels of proteasome inhibition have been observed at next scheduled dosing. In theory, this advantage allows cells to recover proteasome activity for normal cellular housekeeping functions between doses.

The relationship between VELCADE plasma concentrations and proteasome inhibition can be described by a maximum effect (E_{max}) model. The E_{max} curve is initially very steep, with small changes in plasma VELCADE concentration over the range of 0.5 to 2.0 ng/mL relating to large increases in the percent inhibition (0–60%). After that, a plateau occurs where marginal increases of proteasome inhibition are observed in spite of large changes in plasma VELCADE concentrations.

1.2.5 Clinical Experience in Oncology

It is estimated that more than 100,000 patients have been treated with VELCADE, including subjects treated through Millennium-sponsored clinical trials, Investigator-Initiated Studies, the US NCI Cancer Therapy Evaluation Program (CTEP), and with commercially available drug. VELCADE has been commercially available since 13 May 2003.

The overall goal of the Millennium phase 1 program was to determine the MTD and dose-limiting toxicity (DLT) of VELCADE in a number of therapeutic settings involving subjects with various advanced malignancies. In a Phase I trial in subjects with refractory hematologic malignancies, the MTD for a twice weekly for 4 weeks of a 42 day cycle was 1.04 mg/m^2/dose, with dose-limiting toxicities (DLTs) of thrombocytopenia, hyponatremia, hypokalemia, fatigue, and malaise (Orlowski et al., 2002). The toxicity was greatest during the third and fourth weeks of therapy. In the 3-week schedule of VELCADE monotherapy (4 doses, given on Days 1, 4, 8, and 11 of a 21-day treatment cycle), the DLT occurred at 1.56 mg/m^2/dose (3 subjects with Grade 3 diarrhea and 1 with peripheral sensory neuropathy). Therefore, the MTD at this schedule was 1.3 mg/m^2/dose. In a 35-day treatment cycle with 4 weekly doses of VELCADE monotherapy, the MTD was 1.6 mg/m^2/dose and DLT included hypotension, tachycardia, diarrhea, and syncope.

In phase 1 clinical studies, anti-tumor activity was reported in subjects with NHL, multiple myeloma, Waldenström's Macroglobulinemia, squamous cell carcinoma of the nasopharynx, bronchoalveolar carcinoma of the lung, renal cell carcinoma, and prostate cancer.

The safety and efficacy of VELCADE in subjects with multiple myeloma were investigated in two phase 2 clinical studies, studies M34100-024 (subjects with first relapse) (Jagannath et al, 2004) and M34100-025 (subjects with second or greater relapse and refractory to their last prior therapy) (Richardson et al, 2003). In M34100-025, 202 heavily pre-treated subjects with refractory multiple myeloma after at least 2 previous treatments received VELCADE, 1.3 mg/m^2 on Days 1, 4, 8, and 11 of a 21-day treatment cycle. The European Group for Blood and Marrow Transplant (EBMT) response criteria, as described by Blade (Blade et al., 1998) were utilized to determine disease response. CRs were observed in 4% of subjects, with an additional 6% of subjects meeting all criteria for CR but having a positive immunofixation test. PR or better was observed in 27% of subjects, and the overall response rate (CR, PR and minor response [MR] combined) was 35%. Seventy percent of subjects experienced stable disease or better.

The phase 3 study (M34101-039) (Richardson et al, 2005), also referred to as the APEX study,

was designed to determine whether VELCADE provided benefit (time to progression [TTP], response rate, and survival) to subjects with relapsed or refractory MM relative to treatment with high-dose dexamethasone. The study was also designed to determine the safety and tolerability of VELCADE relative to high-dose dexamethasone, and whether treatment with VELCADE was associated with superior clinical benefit and quality of life relative to high-dose dexamethasone. A total of 669 subjects were enrolled and 663 subjects received study drug (VELCADE: 331; dexamethasone: 332). Subjects randomized to VELCADE received 1.3 mg/m^2 I.V. push twice weekly on days 1, 4, 8, and 11 of a 3-week cycle for up to eight treatment cycles as induction therapy, followed by 1.3 mg/m^2 VELCADE weekly on days 1, 8, 15, and 22 of a 5-week cycle for three cycles as maintenance therapy. Subjects randomized to dexamethasone received oral dexamethasone 40 mg once daily on days 1 to 4, 9 to 12, and 17 to 20 of a 5-week cycle for up to four treatment cycles as induction therapy, followed by dexamethasone 40 mg once daily on days 1 to 4 followed of a 4-week cycle for five cycles as maintenance therapy. The European Group for Blood and Marrow Transplant (EBMT) response criteria, as described by Blade (Blade et al., 1998) were utilized to determine disease response. There was a 78% increase in TTP for the VELCADE arm. Median TTP was 6.2 months for the VELCADE arm and 3.5 months for the dexamethasone arm (P<.0001). CR (complete response) + PR (partial response) was 38% with VELCADE vs. 18% with dexamethasone (P<.0001). CR was 6% with VELCADE vs. <1% with dexamethasone (P<.0001). The CR + nCR rate was13% with VELCADE vs. 2% with dexamethasone. In subjects who had received only one prior line of treatment (VELCADE: 132; dexamethasone: 119), CR + PR was 45% with VELCADE vs. 26% with dexamethasone (P=.0035). With a median 8.3 months of follow-up, overall survival was significantly longer (P=.0013) for subjects on the VELCADE arm vs. subjects on the dexamethasone arm. The probability of survival at one year was 80% for the VELCADE arm vs. 66% for the dexamethasone arm, which represented a 41% decreased relative risk of death in the first year with VELCADE (P=.0005). In subjects who had received only one prior line of treatment, the probability of survival at one year was 89% for the VELCADE arm vs. 72% for the dexamethasone arm, which represented a 61% decreased relative risk of death in the first year with VELCADE (P=.0098). Updated response rates and survival data were reported for M34101-039 (Richardson ASH, 2005). The updated CR (complete response) + PR (partial response) rate was 43% with VELCADE. The CR + nCR rate was 16% with VELCADE. With a median 22 months of follow-up, overall survival was significantly longer for subjects on the VELCADE arm vs. subjects on the dexamethasone arm. The median overall survival was 29.8 months (95% CI: 23.2, not estimable) for the VELCADE arm vs 23.7 months (95% CI: 18.7, 29.1) for the dexamethasone arm (hazard ratio = 0.77, P= 0.0272). The probability of survival at one year was 80% for the VELCADE arm vs. vs 67% for the dexamethasone arm (P=0.0002). Studies using VELCADE as monotherapy and in combination with other chemotherapy agents are continuing.

1.2.6 Potential Risks of VELCADE

To date, more than 100,000 patients have been treated with VELCADE in both clinical trials investigating its use in hematological malignancies and solid tumors, and in patients who were treated with commercially available VELCADE.

Table 1-1 Known Anticipated Risks of VELCADE by MedDRA System Organ Class, Observed Incidence, and Preferred Term

System Organ Class Observed Incidence	Preferred Term
Blood and Lymphatic System Disorders	
Most common	Thrombocytopenia *, anaemia*
Very common	Neutropenia*
Common	Lymphopenia, pancytopenia*, leukopenia*, febrile neutropenia
Cardiac Disorders	
Common	Tachycardia, atrial fibrillation, palpitations, cardiac failure congestive*
Uncommon	Cardiogenic shock*, , atrial flutter, cardiac tamponade*±, bradycardia, atrioventricular block complete,, arrhythmia, cardiac arrest, cardiac failure, arrhythmia, pericardial effusion, pericarditis, pericardial disease±, cardiopulmonary failure±
Ear and Labyrinth Disorders	
Uncommon	Deafness, hearing impaired
Eye Disorders	
Common	Blurred vision, conjunctivitis, conjunctival haemorrhage
Gastrointestinal Disorders	
Most common	Constipation, diarrhoea*, nausea, vomiting*
Very common	Abdominal pain (excluding oral and throat)
Common	Dyspepsia, pharyngolaryngeal pain, gastroesophageal reflux, abdominal distension, gastritis, stomatitis, mouth ulceration, dysphagia, gastrointestinal haemorrhage *, lower gastrointestinal haemorrhage*±, rectal haemorrhage
Uncommon	Eructation, gastrointestinal pain, tongue ulceration, retching, upper gastrointestinal haemorrhage*, haematemesis*, oral mucosal petechiae, ileus paralytic*, ileus, odynophagia, enteritis, colitis, oesophagitis, , enterocolitis, diarrhoea haemorrhagic, acute pancreatitis*, intestinal obstruction
General Disorders and Administration Site Conditions	
Most common	Fatigue, pyrexia
Very common	Chills, oedema peripheral, asthenia
Common	Neuralgia, lethargy, malaise, chest pain, mucosal inflammation*
Uncommon	Injection site pain, injection site irritation, injection site phlebitis, general physical health deterioration*, catheter-related complication
Hepatobiliary Disorders	
Uncommon	Hyperbilirubinaemia, hepatitis*±
Immune System Disorders	
Uncommon	Drug hypersensitivity, angioedema

Table 1-1 Known Anticipated Risks of VELCADE by MedDRA System Organ Class, Observed Incidence, and Preferred Term

System Organ Class Observed Incidence	Preferred Term
Infections and Infestations	
Very common	Upper respiratory tract infection, nasopharyngitis, , pneumonia*, Herpes zoster*
Common	Lower respiratory tract infection*, sinusitis, pharyngitis, oral candidiasis, urinary tract infection*,, sepsis*,bactaeremia*, cellulitis*,, Herpes simplex, bronchitis, gastroenteritis*
Uncommon	Septic shock*, catheter-related infection*, skin infection*, Herpes zoster disseminated*, lung infection*, infusion site cellulitis, catheter site cellulitis, infusion site infection, urosepsis*, aspergillosis*, tinea infection, Herpes zoster ophthalmic, Herpes simplex ophthalmic, meningoencephalitis herpetic±, varicella, empyema±, fungal oesophagitis±
Injury, Poisoning, and Procedural Complications	
Uncommon	Subdural haematoma
Investigations	
Common	Weight decreased, alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, blood alkaline phosphatase increased, liver function test abnormal, blood creatinine increased*
Uncommon	Gamma-glutamyltransferase (GGT) increased, oxygen saturation decreased*, blood albumin decreased, ejection fraction decreased*
Metabolism and Nutritional Disorders	
Very common	Decreased appetite, anorexia, dehydration*
Common	Hyperglycaemia, hypoglycaemia, hyponatraemia, hypokalaemia, hypercalcaemia*
Musculoskeletal and Connective Tissue Disorders	
Very common	Bone pain, myalgia, arthralgia
Uncommon	Limb discomfort
Neoplasms, Benign, Malignant, and Unspecified (including cysts and polyps)	
Uncommon	Tumor lysis syndrome*
Nervous System Disorders	
Most common	Peripheral neuropathy (including all preferred terms under the MedDRA high-level term peripheral neuropathy NEC)
Very common	Paresthesia, dizziness excluding vertigo; headache
Common	Polyneuropathy, syncope, dysesthesia, dysgeusia, postherpetic neuralgia
Uncommon	Convulsions, loss of consciousness, ageusia, encephalopathy, paralysis*, autonomic neuropathy, reversible posterior leukoencephalopathy syndrome±

Table 1-1 Known Anticipated Risks of VELCADE by MedDRA System Organ Class, Observed Incidence, and Preferred Term

System Organ Class Observed Incidence	Preferred Term
Psychiatric Disorders	
Very common	Anxiety, insomnia
Common	Confusional state
Uncommon	Delirium
Renal and Urinary Disorders	
Common	Renal impairment*, renal failure*, haematuria
Uncommon	Micturition disorder
Respiratory, Thoracic, and Mediastinal Disorders	
Very common	Cough, dyspnoea
Common	Epistaxis, dyspnoea exertional, pleural effusion*, rhinorrhea, hypoxia*, pulmonary oedema*
Uncommon	Hemoptysis*, acute respiratory distress syndrome*, respiratory failure*, pneumonitis*, lung infiltration, pulmonary alveolar haemorrhage*, interstitial lung disease*, pulmonary hypertension*, pleurisy, pleuritic pain
Skin and Subcutaneous Tissue Disorders	
Very common	Rash
Common	Rash pruritic, rash erythematous, urticaria, petechiae
Uncommon	Cutaneous vasculitis, leukocytoclastic vasculitis±
Vascular Disorders	
Common	Hypotension*, Orthostatic hypotension
Uncommon	Cerebral haemorrhage*

Most common = ≥ 30%, Very common = 10% to 29%, Common=1% to 9%, Uncommon= < 1%,
* Fatal outcomes have been reported.
± Indicates a Preferred term not listed in the source table, however the event is deemed medically important and so is included.
Source: VELCADE Investigator's Brochure, Version 12

Table 1-2 Reports of Adverse Reactions from Postmarketing Experience

System Organ Class Preferred Term	Observed Incidence[a]
Blood and lymphatic system disorders	
Disseminated intravascular coagulation	Rare
Cardiac Disorders	
Atrioventricular block complete	Rare
Cardiac tamponade	Rare
Ear and labyrinth disorders	
Deafness bilateral	Rare
Eye Disorders	
Ophthalmic herpes	Rare
Gastrointestinal Disorders	
Acute pancreatitis	Rare
Ischemic colitis	Rare
Hepatobiliary disorders	
Hepatitis	Uncommon
Liver failure	Unknown
Infections and infestations	
Herpes meningoencephalitis	Rare
Septic Shock	Rare
Immune System Disorders	
Angioedema	Rare
Nervous System Disorders	
Autonomic neuropathy	Rare
Dysautonomia	Unknown
Encephalopathy	Rare
Respiratory, thoracic and mediastinal disorders:	
Acute diffuse infiltrative pulmonary disease[b]	Rare
Acute respiratory distress syndrome (ARDS)	Rare
Interstitial pneumonia	Rare
Lung infiltration	Rare
Pneumonitis	Rare
Pulmonary hypertension	Rare
Skin and subcutaneous system disorders	
Toxic epidermal necrolysis	Unknown

a Incidence is assigned using the following convention: very common (>1/10); common (>1/100 and <1/10); uncommon (>1/1000 and <1/100); rare (>1/10,000 and <1/1000); very rare (<1/10,000, including isolated reports).

b Acute diffuse infiltrative pulmonary disease is a MedDRA Lower Level Term which corresponds to a Preferred Term of Interstitial lung disease.

Source: VELCADE Investigator's Brochure, Version 12

Other medical events of interest that are considered not causally related to VELCADE include hepatic failure and QT prolongation. Fatal outcomes have been reported.

Women of childbearing potential should avoid becoming pregnant while being treated with VELCADE. Genotoxicity testing has shown that VELCADE is negative in the *in vitro* Ames assay and in the *in vivo* micronucleus assay, but it is a clastogen in the in vitro chromosomal aberration assay.

Additional details on the potential risks of VELCADE may be found in the Investigator's Brochure.

1.3 Study rationale and selection of drug doses

In vitro data show that VELCADE has antitumor activity via the following mechanisms: directly induces apoptosis of multiple myeloma cells, inhibits activation of NF-κB in multiple myeloma cells and in tumor microenvironment, blocks production and intracellular signaling of IL-6.

Clinical trials of VELCADE in renal transplant subjects without cancer suggest that it has activity against non-malignant plasma cells. Proteasome inhibition by VELCADE induced apoptosis of non-malignant human plasma cells and facilitated the treatment of antibody-mediated humoral rejection of kidney allografts (Perry et al., 2008). In combination with immunosuppressive medications for treating antibody-mediated and cell-mediated acute rejection, VELCADE therapy reduced the levels of donor-specific antibodies with minimal toxicity in renal transplant recipients (Everly et al., 2008). Abrogation of anti-HLA alloantibodies were successfully achieved with VELCADE therapy in sensitized renal transplant recipients (Trivedi et al., 2009).

In IgA nephropathy, abnormal pIgA1 immunoglobulins are produced by plasma cells in the bone marrow and tonsils of subjects (Barratt et al., 2005). These aberrant pIgA1 antibodies have a tendency to form immune complexes in the mesangium and induce an inflammatory response via the NF-κB pathway (Ashizawa et al., 2003). An intra-renal autoimmune response characterized by production of cytokines (such as IL-6), growth factors, and adhesion molecules are thought to be the cause of progressive renal damage in IgA nephropathy (Lai et al., 2009). The ubiquitin-proteasome pathway facilitates the translocation of transcription factor NF-κB from the cytosol (where it constitutively resides complexed to its inhibitory protein IκB) into the nucleus. The human kidney proteasome (fully inducible to become iPS) has been purified and characterized confirming the observation that the kidney is primed and predisposed to inflammatory response in autoimmune glomerular diseases (Baldovino et al., 2006). Subjects with significant

proteinuria not in remission from IgA nephropathy were found to have iPS detected in PBMCs (Coppo et al., 2009). Taken together, there is mounting evidence to support the use of proteasome inhibitor therapy for aggressive IgA nephropathy.

Investigators in kidney transplant pilot trials provided 4 doses of VELCADE (1 cycle) for treating renal transplant rejection (Perry et al., 2008; Everly et al., 2008; Trivedi et al., 2009). We propose similar doses (1 cycle on days 1, 4, 8, 11) for induction therapy in subjects with IgA nephropathy. An additional cycle will be given to non-responders following VELCADE induction therapy.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to investigate ability of VELCADE to induce complete or partial remission in subjects with severe IgA nephropathy and risk factors for progression of disease. Complete remission is defined as proteinuria of less than or equal to 300 mg per day. Partial remission is defined as reduction in daily proteinuria of greater than 50% from baseline (enrollment) proteinuria. A clinical relapse is defined as a rise in daily proteinuria of greater than 50% from nadir following successful induction therapy. A safety analysis of the use of VELCADE in this study population will be performed.

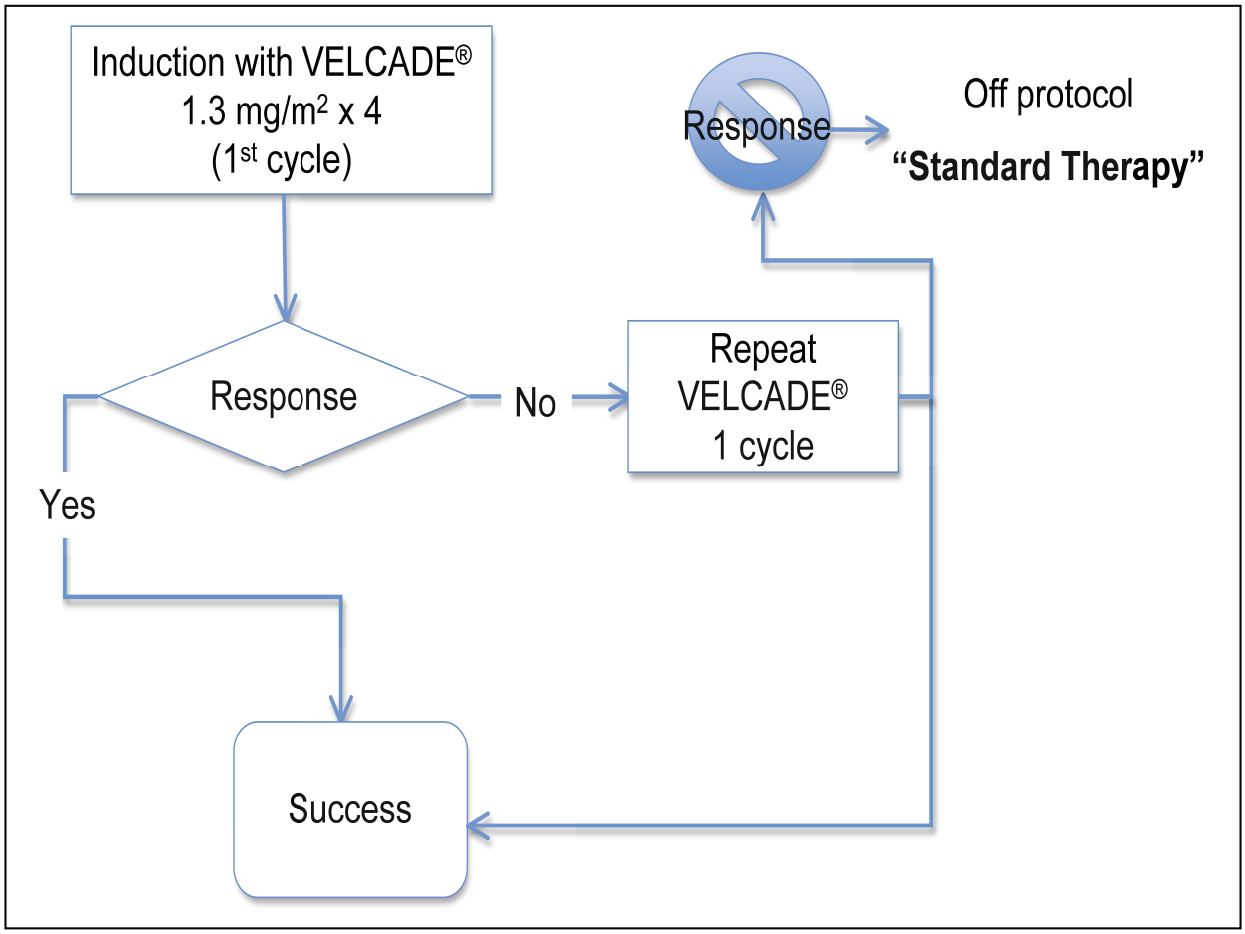
2.2 Secondary Objectives

The secondary objectives of this study are to assess clinical outcomes relating to safety and efficacy, such as infection, malignancy, preservation of renal function, and reduction in the requirement of anti-hypertensive drugs; and to study mechanistic assays to predict remission. The proportion of subjects with less than 50% reduction in daily proteinuria or partial responders will be assessed.

3 INVESTIGATIONAL PLAN

3.1 Overall Design and Plan of the Study

This trial is a single center, open-label, single treatment group assignment, safety and efficacy pilot study that will enroll 10 subjects with severe IgA nephropathy. Participants will receive 4 doses of VELCADE (1 cycle) to induce clinical remission. Non-responders after a 4-week observation period will receive a second successive cycle of VELCADE. Subjects who do not have any response to VELCADE after 2 cycles will be considered treatment failure. They will be taken off the protocol and receive standard renal care by their physicians. Responders will be followed for clinical relapse. No additional cycles of VELCADE will be provided after a relapse per protocol. Subjects do have the option to receive VELCADE as an off-label therapy after discussion with their physicians and be taken off the protocol. Subjects will be followed for 1 year after enrollment.



The primary endpoint will be proportion of participants achieving complete or partial remission (see section 2.1 for definition of remission). A safety analysis will be included in the primary endpoint. The secondary endpoints include proportion of subjects with infection, malignancy,

deterioration of renal function, and reduction in the requirement of anti-hypertensive drugs. The proportion of subjects with partial response or clinical relapse will also be assessed (see sections 2.1 and 2.2 for definitions of partial responders and clinical relapse).

A study flow chart is provided in section 8.1. Subjects with toxicities will be followed until the toxicity resolves or returns to baseline. VELCADE may be administered within ± 1 day of the dosing schedule (at least 72 hrs must elapse between VELCADE doses). For follow-up study visits after the administration of VELCADE, a window of ± 5 days will be allowed.

3.2 Selection of Subjects

The total number of subjects to be enrolled on this study is 10.
Enrollment is defined as the first day of VELCADE treatment (i.e., Day 1 of cycle 1).

3.2.1 Inclusion Criteria

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

1. Male or female, 18 years of age or older.
2. Subject is capable of understanding the purposes and risks of the study, is willing to participate in and comply with the study, and can give voluntary written informed consent before performance of any study-related procedure not part of normal medical care, with the understanding that consent may be withdrawn by the subject at any time without prejudice to future medical care.
3. Female subject is either post-menopausal or surgically sterilized or willing to use an acceptable method of birth control (i.e., a hormonal contraceptive, intra-uterine device, diaphragm with spermicide, condom with spermicide, or abstinence) for the duration of the study.
4. Male subject agrees to use an acceptable method for contraception for the duration of the study.
5. Subjects must have biopsy proven severe IgA nephropathy.
6. Within 14 days before enrollment, creatinine clearance as measured by MDRD formula must be greater or equal to 30 cc/min/1.73 m^2.
7. Prior to enrollment, quantified proteinuria (via 24 hr urine collection or spot urine protein and creatinine ratio) must be greater or equal to 1000 mg.
8. Unless contraindicated subject must be on stable doses of ACEI and/or ARB and/or renin inhibitor for at least 4 weeks prior to screening.

3.2.2 Exclusion Criteria

Subjects meeting any of the following exclusion criteria are not to be enrolled in the study.

1. Subject has a platelet count of less than 30×10^9/L within 14 days before enrollment.
2. Subject has an absolute neutrophil count of less than 1.0×10^9/L within 14 days before enrollment.
3. Subject has ≥Grade 2 peripheral neuropathy within 14 days before enrollment.

4. Myocardial infarction within 6 months prior to enrollment or has New York Heart Association (NYHA) Class III or IV heart failure (see section 8.3), uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities. Prior to study entry, any ECG abnormality at screening has to be documented by the investigator as not medically relevant.
5. Subject has hypersensitivity to VELCADE, boron or mannitol.
6. Female subject is pregnant or breast-feeding. Confirmation that the subject is not pregnant must be established by a negative serum β-human chorionic gonadotropin (β-hCG) pregnancy test result obtained during screening. Pregnancy testing is not required for post-menopausal or surgically sterilized women.
7. Subject has received other investigational drugs within 14 days before enrollment.
8. Serious medical conditions and infections (including HIV, HCV, HBV) or psychiatric illness likely to interfere with participation in this clinical study, as determined by review of the medical history.
9. Diagnosed or treated for another malignancy within 3 years of enrollment, with the exception of complete resection of basal cell carcinoma or squamous cell carcinoma of the skin, an in situ malignancy, or low-risk prostate cancer after curative therapy.
10. Subject has total bilirubin greater than 1.5 x upper limit of normal.

3.3 Study Treatments

3.3.1 Clinical Trial Materials

VELCADE for injection is a sterile lyophilized powder for reconstitution and is supplied in vials containing VELCADE and mannitol at a 1:10 ratio. For example, vials containing 3.5 mg of VELCADE contain 35 mg of mannitol.

3.3.2 Preparation, Handling, and Storage of Drugs

VELCADE

Vials containing lyophilized VELCADE for Injection should be stored according to the label requirements. For the United States, store at USP Controlled Room Temperature which is 25ºC (77ºF); excursions permitted from 15 to 30ºC (59 to 86ºF). To date, stability data indicate that the lyophilized drug product is stable for at least 18 months when stored under the recommended conditions. Stability studies are ongoing, and Millennium Pharmaceuticals, Inc. will notify the investigator should this information be revised during the conduct of the study.

VELCADE is cytotoxic. As with all cytotoxic drugs, caution is required when preparing and handling VELCADE solutions. Cytotoxic drugs should only be handled by staff specially trained in the safe handling of such preparations. The use of gloves and other appropriate protective clothing is recommended. In case of skin contact, wash the affected area immediately and thoroughly with soap and water for at least 15 minutes. If product contacts eye, immediately flush eye thoroughly with water for at least 15 minutes. Always contact a physician after any

form of body contact. All materials that have been used for preparation should be disposed of according to standard practices. A log must be kept of all disposed materials.

Drug is available in sterile, single use vials containing 3.5 mg of VELCADE. Each vial of VELCADE for Injection should be reconstituted under a laminar flow biological cabinet (hood) within eight hours before dosing with 3.5 mL of normal (0.9%) saline, Sodium Chloride Injection USP, so that the reconstituted solution contains VELCADE at a concentration of 1 mg/mL. Prior to reconstitution the vials should remain in the cartons to protect them from light. Dissolution is completed in approximately 10 seconds. The reconstituted solution is clear and colorless, with a final pH of 5 to 6. Reconstituted VELCADE should be administered promptly and in no case more than 8 hours after reconstitution. All materials that have been used for preparation should be disposed of according to standard practices. A log must be kept of all disposed materials.

VELCADE Administration and Dosage Schedule

VELCADE is to be administered (1 cycle) at a dose level of 1.3mg/m^2 on days 1, 4, 8, 11 for induction. A second cycle may be repeated for subjects who have not responded within 30 days after the induction cycle. VELCADE may be administered within a window of ± 1 day but must be given at least 72 hours after the previous VELCADE dose. Drug will be administered only to eligible subjects under the supervision of the investigator or identified sub-investigator(s). Subjects may be treated on an outpatient basis, if possible. The pharmacist will prepare the drug under aseptic conditions. The amount (in mg) of drug to be administered will be determined based on body surface area. Body surface area is to be calculated based on body weight using a standard nomogram (see section 8.2). The dose should be calculated on Day 1 of each cycle; the dose administered should remain the same throughout each cycle but should be recalculated at the start of the next cycle. If a subject experiences a notable change in weight (e.g., loss or gain of ≥8 lbs or 3.6 kg) within a cycle, as determined by an unscheduled weight assessment, then the subject's dose should be recalculated at that time.
The appropriate amount of VELCADE will be drawn from the injection vial and administered as an intravenous (IV) push over 3 to 5 seconds followed by a standard saline flush or through a running IV line. Vials are for single use administration.

3.3.3 Dose Modification and Delay

Dose escalation will not be allowed in any subject, and there must be at least 72 hours between each dose of VELCADE.

Before each drug dose, the subject will be evaluated for possible toxicities that may have occurred after the previous dose(s). Toxicities are to be assessed according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0 (see section 8.5).

All previously established or new toxicities observed at any time, with the exception of neuropathic pain and peripheral sensory neuropathy, are to be managed as follows:

- If the subject experiences febrile neutropenia, a Grade 4 hematologic toxicity (including a platelet count $<25 \times 10^9$/L) or any ≥Grade 3 non-hematologic toxicity considered by the investigator to be related to VELCADE, then drug is to be held.

- For non-hematologic toxicities, VELCADE is to be held for up to 2 weeks until the toxicity returns to Grade 1 or better.

- For hematologic toxicities, VELCADE is to be held for up to 2 weeks until the subject has a hemoglobin value of 8.0 g/dL, platelet value of 30×10^9/L, and absolute neutrophil value of 1.0×10^9/L.

- Dose interruption or study discontinuation is **not** required for lymphopenia of any grade.

- If, after VELCADE has been held, the toxicity does not resolve, as defined above, then drug must be discontinued.

If the toxicity resolves, as defined above, and VELCADE is to be restarted, the dose must be reduced by approximately 25% as follows:

- If the subject was receiving 1.3 mg/m^2, reduce the dose to 1.0 mg/m^2.
- If the subject was receiving 1.0 mg/m^2, reduce the dose to 0.7 mg/m^2.
- If the subject was receiving 0.7 mg/m^2, discontinue drug, unless subject is responding, in which case this should be discussed with the PI. Dose reductions below 0.7 mg/m^2 should be avoided, but will be considered if subject is having a good response.

Subjects who experience VELCADE-related neuropathic pain and/or peripheral sensory neuropathy are to be managed as presented in Table 3.1 Management of Patients with VELCADE-Related Neuropathic Pain and/or Peripheral Sensory Neuropathy.

Table 3-1 Management of Patients with VELCADE Related Neuropathic Pain and/or Peripheral Sensory or Motor Neuropathy

Recommended Dose Modification for VELCADE related Neuropathic Pain and/or Peripheral Sensory or Motor Neuropathy	
Severity of Peripheral Neuropathy Signs and Symptoms	**Modification of Dose and Regimen**
Grade 1 (paresthesias, weakness and/or loss of reflexes) without pain or loss of function	No action
Grade 1 with pain or Grade 2 (interfering with function but not with activities of daily living)	Reduce VELCADE to 1.0 mg/m^2
Grade 2 with pain or Grade 3 (interfering with activities of daily living)	Withhold* VELCADE therapy until toxicity resolves. When toxicity resolves reinitiate with a reduced dose of VELCADE at 0.7mg.m^2 and change treatment schedule to once per week.*
Grade 4 (Sensory neuropathy which is disabling or motor neuropathy that is life threatening or leads to paralysis)	Discontinue VELCADE
Grading based on NCI Common Terminology Criteria CTCAE v3.0 NCI Common Terminology Criteria website - http://ctep.info.nih.gov/reporting/ctc.html	

ADL = activities of daily living

*Key:

Reduce by one dose level: VELCADE dose reduction from 1.3 to 1.0, or 1.0 to 0.7 mg/m^2/dose.

Reduce by two dose levels: VELCADE dose reduction from 1.3 or 1.0 to 0.7 mg/m^2/dose.

Hold: Interrupt VELCADE for up to 2 weeks until the toxicity returns to Grade 1 or better.

Schedule change: Schedule change from VELCADE twice per week (Days 1, 4, 8 and 11 on a Q3W cycle) to once per week (Days 1, 8, 15, and 22 on a Q5W cycle). If the treatment schedule is already once weekly, then it should remain once weekly.

The neurotoxicity-directed questionnaire (see section 8.6) is a useful tool for determining the presence and intensity of neuropathic pain and/or peripheral neuropathy from the subject's perspective. Neuropathic symptoms are more prominent than abnormalities on the clinical examination. After the subject completes the neurotoxicity-directed questionnaire, the questionnaire should be reviewed to assist with the evaluation of the onset and intensity of peripheral neuropathy and other neurotoxicities that may possibly require intervention or dose modification.

Dosage in Subjects with Hepatic Impairment

Subjects with mild hepatic impairment do not require a starting dose adjustment and should be treated per the recommended VELCADE dose. Subjects with moderate or severe hepatic impairment should be started on VELCADE at a reduced dose of 0.7 mg/m^2 per injection during the first cycle, and a subsequent dose escalation to 1.0 mg/m^2 or further dose reduction to 0.5 mg/m^2 may be considered based on subject tolerance (see **Table 3)**.

Table 3: Recommended Starting Dose Modification for VELCADE in Patients with Hepatic Impairment

Bilirubin Level	SGOT (AST) Levels		Modification of Starting Dose
Mild	≤ 1.0x ULN	> ULN	None
	> 1.0x−1.5x ULN	Any	None
Moderate	> 1.5x−3x ULN	Any	Reduce VELCADE to 0.7 mg/m^2 in the first cycle. Consider dose escalation to 1.0 mg/m^2 or further dose reduction to 0.5 mg/m^2 in subsequent cycles based on patient tolerability.
Severe	> 3x ULN	Any	

3.3.4 Treatment Assignment

This trial is a single center and open-label with single treatment group assignment.

3.3.5 Blinding, Packaging, and Labeling

VELCADE will be supplied in vials as open-label stock. Both the box label and vial label will fulfill all requirements specified by governing regulations.

3.3.6 Concomitant Treatment

Prophylaxis

Subjects will be given oral acyclovir within the first month after enrollment for a total of six months as a prophylactic agent to prevent reactivation of varicella zoster virus (shingles). Oral acyclovir will be dosed at 400mg daily (Pour et al., 2009).

Titration of Concurrent Therapy

The following medications should not be titrated up (or increased) during the duration of the study:

- ACEI
- ARB
- Renin inhibitor

Prohibited Concurrent Therapy

- Any investigational agent other than VELCADE.

3.3.7 Treatment Compliance

All drugs will be administered to eligible subjects under the supervision of the investigator or identified sub-investigator(s). The pharmacist will maintain records of drug receipt (if applicable), drug preparation, and dispensing, including the applicable lot numbers, subjects' height, body weight, and body surface area (see section 8.2), and total drug administered in milliliters and milligrams. Any discrepancy between the calculated dose and dose administered and the reason for the discrepancy must be recorded in the source documents.

3.4 Duration of Treatment and Subject Participation

Subjects will be screened for eligibility to participate in the study. Treatment consists of up to 2 cycles of VELCADE infusion if required (see section 3.1). A single cycle of treatment is comprised of four doses of VELCADE infusion over a 2-week period. Subjects will be followed for 1 year after enrollment if they qualify to participate in the trial. Enrollment is defined as the first day of VELCADE treatment (i.e., Day 1 of cycle 1).

3.5 Termination of Treatment and/or Study Participation

Subjects 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 also has the right to withdraw subjects from the study for any of the following reasons:

- Intercurrent illness
- Occurrence of an unacceptable adverse event
- A treatment cycle delay or VELCADE interruption of >2 weeks or missing three of four VELCADE doses within a treatment cycle because of toxicity
- Subject request
- Protocol violations
- Non-compliance
- Administrative reasons
- Failure to return for follow-up
- General or specific changes in the subject's condition unacceptable for further treatment in the judgment of the investigator

- Progressive disease at any time (including worsening of serum creatinine)

At the time of withdrawal, all study procedures outlined for the End of Study visit (Month 12) should be completed. The primary reason for a subject's withdrawal from the study is to be recorded in the source documents.

Participants who are non-responders prior to or following the second successive cycle of VELCADE may choose to return to their physicians for further care and be taken off the protocol.

3.6 Efficacy, Pharmacodynamic/Pharmacogenomic/Correlative studies, and Safety Measurements

3.6.1 Efficacy Measurements

Quantification of urinary protein will be made after treatment to assess primary and secondary endpoints. Other variables to be assessed for secondary endpoints include blood pressure, hematuria (urinalysis), and serum creatinine.

3.6.2 Safety Measurements

The following variables will be monitored after enrollment:

1) Complete blood count

2) Liver function test

3) Serum immunoglobulin profile

4) Renal function (24 hr urine creatinine clearance)

5) Serum uric acid

6) Clinical signs of infections

4 ADVERSE EVENTS

4.1 Definitions

4.1.1 Adverse Event Definition

An **adverse event** (AE) is any untoward medical occurrence in a subject administered a pharmaceutical product, which does not necessarily have a causal relationship with the treatment. An adverse event can be any unfavorable and unintended sign (e.g., including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the drug, whether or not it is considered to be drug related. This includes any newly occurring event or previous condition that has increased in severity or frequency since the administration of drug.

4.1.2 Serious Adverse Event Definition

A **serious adverse event** (SAE) is any adverse event, occurring at any dose and regardless of causality that:

- Results in **death**.
- Is **life-threatening**. Life-threatening means that the subject was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- Requires inpatient **hospitalization or prolongation of existing hospitalization**. Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered AEs if the illness or disease existed before the subject was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).
- Results in **persistent or significant disability/incapacity**. Disability is defined as a substantial disruption of a persons' ability to conduct normal life functions.
- Is a congenital anomaly/birth defect.
- Is an **important medical event**. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Clarification should be made between the terms "serious" and "severe" since they ARE NOT synonymous. The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as a severe headache). This is NOT the same as "serious," which is based on subject/event outcome or action criteria described above and are usually associated with events that pose a threat to a subject's life or functioning. A severe

adverse event does not necessarily need to be considered serious. For example, persistent nausea of several hours duration may be considered severe nausea but not an SAE. On the other hand, a stroke resulting in only a minor degree of disability may be considered mild, but would be defined as an SAE based on the above noted criteria. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

4.2 Procedures for AE and SAE Reporting

Investigator-sponsor must report all serious adverse event (SAE) regardless of relationship with any study drug or expectedness to Millennium as soon as possible, but no later than 5 calendar days of the investigator-sponsor's observation or awareness of the event. All sub-investigators must report all SAEs to the investigator-sponsor so that the investigator-sponsor can meet his/her foregoing reporting obligations to Millennium.

Investigator-sponsor must also provide Millennium with a copy of all communications related to the Study or Drug with the applicable regulatory authority, including, but not limited to, telephone conversation logs, as soon as possible but no later than 5 calendar days of that communication.

Millennium's Product Safety Department will send to the investigator-sponsor a monthly listing of the SAE reports received for SAE verification. Investigator-sponsor will be responsible for forwarding such reports to any sub-investigator(s) and providing any follow-up safety information requested by Millennium.

SAE Reporting Contact Information: North America
PPD, Inc.
Safety and Medical Management, US
Fax: +1 888-488-9697
Hotline number (available 24/7): 1-800-201-8725

For both serious and non-serious adverse events, the investigator or sub-investigator must determine both the intensity of the event and the relationship of the event to drug administration.

Relationship to drug administration will be determined by the investigator or sub-investigator responding yes or no to the question: Is there a reasonable possibility that the adverse event is associated with the drug?

Intensity for each adverse event, including any lab abnormality, will be determined by using the NCI CTCAE, version 3.0, as a guideline, wherever possible. The criteria are available online at http://ctep.cancer.gov/reporting/ctc.html.

4.3 Monitoring of Adverse Events and Period of Observation

Adverse events, both serious and non-serious, and deaths that occur during the subject's study participation will be recorded in the source documents. All SAEs should be monitored until they

are resolved or are clearly determined to be due to a subject's stable or chronic condition or intercurrent illness(es).

4.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects she is pregnant while participating in this study, she must inform her treating physician immediately and permanently discontinue drug therapy. Millennium must also be contacted immediately by faxing a completed Pregnancy Form to either Millennium Product Safety for North America or PRA Safety Management Services for rest of world. The pregnancy must be followed through outcome (i.e. delivery, still birth, miscarriage).

5 STATISTICAL PROCEDURES

5.1 Sample Size Estimation

This is a pilot study consisting of 10 subjects. The analyses will be descriptive. However, to the extent possible, estimates obtained in the study will be interpreted in the context of data from historical cohorts.

5.2 Randomization and Stratification

This is an open label and single treatment arm study.

5.3 Populations for Analysis

Adult subjects with IgA nephropathy will be enrolled.

5.4 Procedures for Handling Missing, Unused, and Spurious Data

Subjects whose outcome is unknown will be considered as efficacy failures. There will be no other imputation of missing data.

5.5 Statistical Methods

5.5.1 Baseline Comparisons

Summary descriptive statistics for baseline and demographic characteristics will be collected for all enrolled participants. Demographic data will include age, race, sex, body weight, height, baseline proteinuria, creatinine clearance, and serum creatinine; these data will be presented in the following manner:

1) Continuous data (i.e., age, body weight, and height etc.) will be summarized descriptively by mean, standard deviation, and range.

2) Categorical data (i.e., sex and race) will be presented as enumerations and percentages.

5.5.2 Efficacy Analysis

The following analysis samples will be utilized for statistical analyses:

1) Intent-to-treat (ITT) sample: Any subjects who received a dose of the study drug.

2) Per-protocol (PP) sample: All enrolled subjects who received at least 1 cycle of the study drug and have primary efficacy assessment data.

The proportion of participants who have achieved complete or partial remission or who are partial responders will be analyzed using PP sample and descriptively summarized with a two-sided, 95% CI. Proportion of participants who have improved renal function, less hematuria, and

less anti-hypertensive drug requirements will be analyzed using ITT sample.

5.5.3 Safety Analysis

All subjects who received any study drug will be included in the safety sample. Participants in the safety sample will be included in all safety analyses. All adverse events, including infections, malignancies, morbidity, and various side-effects from the study drug will be reported using CTCAE version 3.0.

5.5.4 Correlative studies

PAXgene™ and serum separator tubes will be used to collect blood samples from participants prior to and after VELCADE therapy. Urine samples will also be collected from participants. mRNA of relevant genes will be analyzed from blood and urine to be used as predictors of response to therapy. Additional correlate assessments may also be performed in the future.

5.6 Data Monitoring

Analysis of primary and secondary endpoints will be performed after 5 subjects have been enrolled.

5.7 Procedures for Reporting Deviations to Original Statistical Analysis Plan

The principal features of the study design and of the plan for statistical analysis of data are outlined in this protocol and in the subsequent statistical analysis plan. Any changes in these principal features will be subject to review by the study sponsor. These changes will be described in the final report as appropriate.

6 ADMINISTRATIVE REQUIREMENTS

6.1 Good Clinical Practice

The study will be conducted in accordance with the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP), FDA regulations and other appropriate regulatory requirement(s). The investigator will be thoroughly familiar with the appropriate use of the drug as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

6.2 Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki (see section 8.4) and Institutional Review Board (IRB) requirements. The IRB will review all appropriate study documentation in order to safeguard the rights, safety and well being of the subjects. The study will only be conducted at sites where IRB approval has been obtained. The protocol, Investigator's Brochure, informed consent, advertisements (if applicable), written information given to the subjects (if applicable), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the investigator. Millennium requests that informed consent documents be reviewed by Millennium or designee prior to IRB submission.

6.3 Subject Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from the subject prior to study participation. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP, IRB, and all applicable regulatory requirement(s).

A separate Authorization Form for subject authorization to use and disclose personal health information under the U.S. Department of Health and Human Services Standards for Privacy of Individually Identifiable Health information (HIPAA), 45 CFR Parts 160 and 164 regulations will also be obtained, as per IRB policy.

6.4 Subject Confidentiality

In order to maintain subject privacy, all data capture records, drug accountability records, study reports and communications will identify the subject by initials and the assigned subject number.

Subject medical information obtained as part of this study is confidential, and must not be disclosed to third parties, except as noted below. The subject may request in writing that medical information is given to his/her personal physician.

The investigator/institution will permit Millennium monitor(s) and auditor(s) or its designees, the FDA and/or other applicable regulatory authority(ies) access to the subject's original medical records for verification of data gathered on the data capture records and to audit the data

collection process. The access may consist of study-related monitoring, audits, IRB reviews, and FDA inspections. Release of research results should preserve the privacy of medical information and must be carried out in accordance with HIPAA regulations. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

6.5 Protocol Compliance

The investigator will conduct the study in compliance with the protocol given approval by the IRB and the appropriate regulatory authority(ies). Changes to the protocol will require approval from Millennium and written IRB approval prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to subjects. The IRB may provide, if applicable regulatory authority(ies) permit, expedited review and approval for minor change(s) in ongoing studies that have the approval of the IRB. The investigator will submit all protocol modifications to Millennium and the regulatory authority(ies) in accordance with the governing regulations.

Any departures from the protocol must be fully documented in the source documents.

6.6 On-site Audits

Regulatory authorities, the IRB and/or Millennium's clinical quality assurance group may request access to all source documents, data capture records, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

6.7 Drug Accountability

Accountability for the drug at all study sites is the responsibility of the principal investigator. The investigator will ensure that the drug is used only in accordance with this protocol. Drug accountability records indicating the drug's delivery date to the site (if applicable), inventory at the site (if applicable), use by each subject, and return to Millennium or disposal of the drug (if applicable and if approved by Millennium) will be maintained by the clinical site. Accountability records will include dates, quantities, lot numbers, expiration dates (if applicable), and subject numbers.

All material containing VELCADE will be treated and disposed of as hazardous waste in accordance with governing regulations.

6.8 Premature Closure of the Study

This study may be prematurely terminated, if in the opinion of the investigator or Millennium, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the investigator or Millennium by the terminating party. Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects
- Failure to enter subjects at an acceptable rate

- Insufficient adherence to protocol requirements
- Insufficient complete and/or evaluable data
- Plans to modify, suspend or discontinue the development of the drug

Should the study be closed prematurely, all study materials must be returned to Millennium.

6.9 Record Retention

The investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s).

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8 APPENDICES

8.1 Study Flow Chart

VELCADE for severe IgA nephropathy[1,2,3]

		1st Cycle							2nd Cycle (if needed)													
Service/Procedure/Activity	Screen	Day 1	Day 4	Day 8	Day 11	Day 18	Day 25	Day 39	Day 43	Day 46	Day 50	Day 53	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12
Physical Exam	X					X	X	X					X	X	X	X	X	X	X	X	X	X	X
AE Assessment	X	X	X	X	X	X	X	X					X	X	X	X	X	X	X	X	X	X	X
Chemistry-10	X	X		X		X	X	X			X		X	X	X	X	X			X			X
Liver Panel	X	X				X	X	X					X	X	X	X	X			X			X
Urinalysis	X						X	X					X	X			X			X			X
Urine Protein/Creatinine	X					X	X	X					X	X		X	X			X			X
Serum Ig Profile	X						X							X			X						X
CBC	X	X		X		X	X	X			X		X	X		X	X			X			X
Serum Uric Acid	X						X										X						X
MDRD Calculation GFR	X						X	X						X			X			X			X
24 Hr Creatinine Clearance	X						X							X			X			X			X
Intervention:																							
VELCADE 1.3 mg/m^2 (1st cycle)		X	X	X	X																		
If needed 2nd cycle of VELCADE									X	X	X	X											
Correlative Studies:																							
Pax Gene Blood Collection	X			X		X	X	X			X		X	X			X			X			X
Serum Tube	X			X		X	X	X			X		X	X			X			X			X
Plasma Tube	X			X		X	X	X	X	X	X	X	X	X			X			X			X
Urine Collection	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

1. Clinical Trial to be conducted at Weill Cornell CTSC except for outpatient visits at The Rogosin Institute on Month(s) 4, 5, 7, 8, 10 and 11.
2. Non-responders will be offered "standard therapy" at the discretion of their physicians.
3. Patients with toxicities to VELCADE will be followed until the toxicity resolves or returns to baseline.

8.2 Body Surface Area and Creatinine Clearance Calculations

Body surface area (BSA) should be calculated using a standard nomogram that yields the following results in meters squared (m^2):

$$\text{BSA} = \sqrt{\frac{Ht(inches) \times Wt(lbs)}{3131}}$$

or

$$\text{BSA} = \sqrt{\frac{Ht(cm) \times Wt(kg)}{3600}}$$

Creatinine clearance (CrCl) can be calculated using the Cockroft-Gault equation as follows:

$$\text{CrCl (ml/min)} = \frac{\text{(140-age) (actual wt in kg)}}{\text{72 x serum creatinine (mg/dl)}}$$

For females use 85% of calculated CrCl value.

Note: In markedly obese subjects, the Cockroft-Gault formula will tend to overestimate the creatinine clearance. (Adipose tissue tends to contribute little creatinine requiring renal clearance.)

8.3 New York Heart Association Classification of Cardiac Disease

The following table presents the NYHA classification of cardiac disease:

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 New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, MA: Little, Brown & Co; 1994:253-256.

8.4 Declaration of Helsinki

World Medical Association Declaration of Helsinki:

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly Helsinki, Finland, June 1964 and amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975 35th WMA General Assembly, Venice, Italy, October 1983 41st WMA General Assembly, Hong Kong, September 1989 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

4. Medical progress is based on research, which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best-proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse

consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

1. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

2. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

3. Appropriate caution must be exercised in the conduct of research, which may affect the environment, and the welfare of animals used for research must be respected.

4. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

5. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

6. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

7. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

8. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

9. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

10. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

11. The subjects must be volunteers and informed participants in the research project.

12. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

13. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

14. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

15. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

16. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

17. Research on individuals from whom it is not possible to obtain consent, including proxy or

advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

18. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

1. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

2. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

3. At the conclusion of the study, every patient entered into the study should be assured of access to the best-proven prophylactic, diagnostic and therapeutic methods identified by the study.

4. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

5. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

8.5 Common Terminology Criteria for Adverse Events Version 3.0

http://ctep.cancer.gov/reporting/ctc.html

8.6 FACT/GOG-Neurotoxicity Questionnaire, Version 4.0

FACT/GOG-Neurotoxicity Questionnaire, Version 4.0

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
I have numbness or tingling in my hands……	0	1	2	3	4
I have numbness or tingling in my feet……	0	1	2	3	4
I feel discomfort in my hands……	0	1	2	3	4
I feel discomfort in my feet……	0	1	2	3	4
I have joint pain or muscle cramps……	0	1	2	3	4
I feel weak all over……	0	1	2	3	4
I have trouble hearing……	0	1	2	3	4
I get a ringing or buzzing in my ears……	0	1	2	3	4
I have trouble buttoning buttons……	0	1	2	3	4
I have trouble feeling the shape of small objects when they are in my hand……	0	1	2	3	4
I have trouble walking……	0	1	2	3	4

Sources: Cella DF, Tulsky DS, Gray G, Sarafian B, Lloyd S, Linn E, et al. The functional assessment of cancer therapy (FACT) scale: development and validation of the general measure. *J Clin Oncol* 1993;11(3):570-79.