PROTOCOL AMENDMENT #1

December 7, 2016

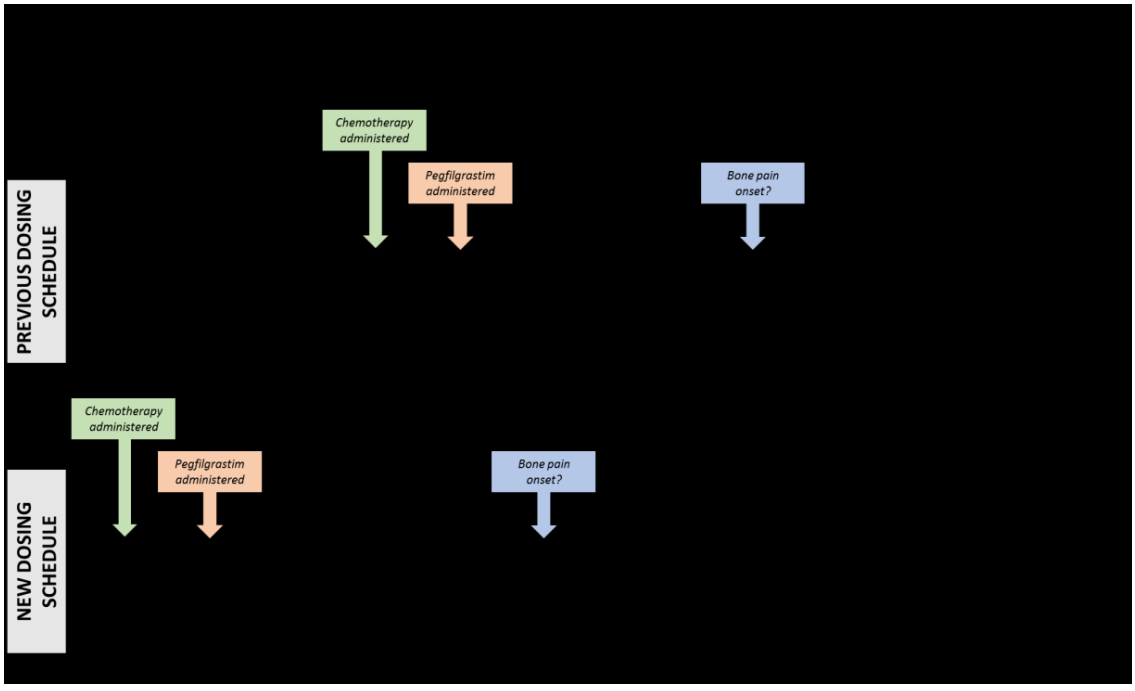
LCCC 1314: A phase II, placebo-controlled, double blind, randomized crossover trial of pregabalin for the prophylaxis of pegfilgrastim-induced bone pain

AMENDMENT INCORPORATES (check all that apply):

___ Editorial, administrative changes
___ Scientific changes (IRB approval)
_X_ Therapy changes (IRB approval)
___ Eligibility Changes (IRB approval)

AMENDMENT RATIONALE AND SUMMARY:

To better support patient accrual into this study, we have made amendments to the dosing schedule of study medication. This new dosing schedule will continue to allow for titration of the study medications, helping to reduce study-related side effects, while still obtaining sufficient drug levels at the estimated time of drug-related bone pain onset (typically 4 days after Neulasta injection; patients will have been given pregabalin 150mg PO BID for at least 48 hours at theoretical onset).



As such, we have made the following amendments to the study protocol (marked in red):

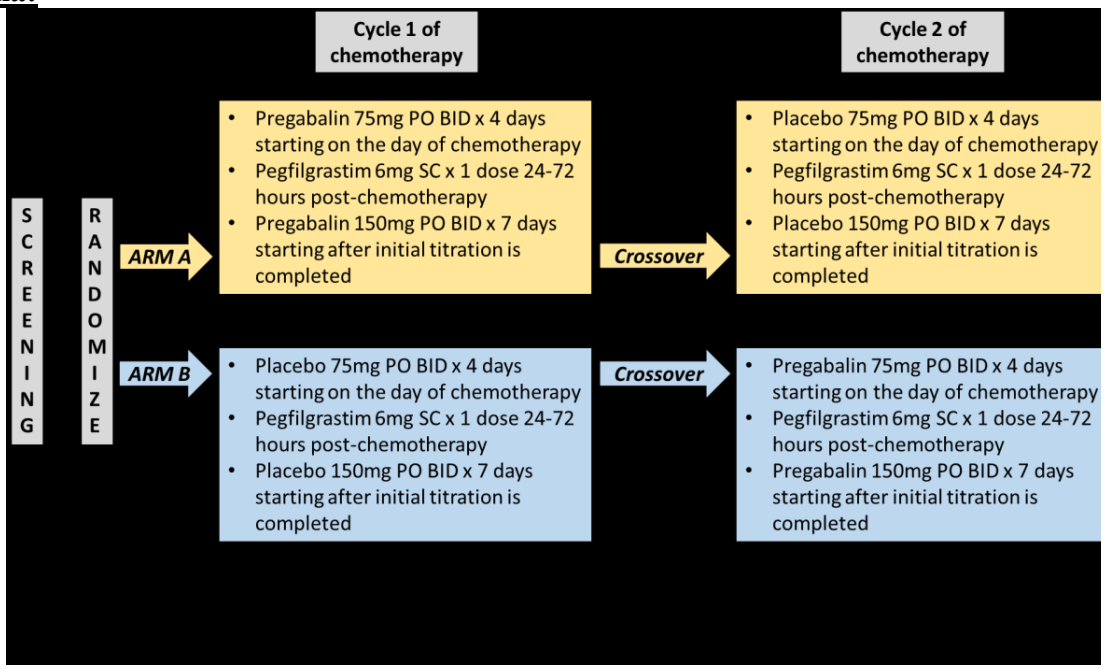
Schedule and Dose of Pregabalin:

1.4.2 Because we are interested in the prevention of pain, the duration of treatment with pregabalin for less than one week prior to pegfilgrastim with continued dosing for 10 days starting from the day of pegfilgrastim administration will be sufficient for primary prophylaxis. See the Treatment Plan example at the front of this protocol for a graphic of dosing of study medication, chemotherapy and pegfilgrastim during a given chemotherapy cycle in a breast cancer patient receiving chemotherapy.

The analgesic effect of pregabalin is dose-responsive often exerting its effect at an average oral dose of 150 mg BID. For all approved indications of pregabalin, patients are generally started at a lower dose (e.g., 75 mg BID), with the dose increased to 150 mg BID to improve tolerance. Therefore, we will start all patients on 75 mg PO BID to begin on the day of chemotherapy prior to increasing the dose to 150 mg PO BID provided the patient is not experiencing >grade 1 pregabalin-associated side effects.

Schema:

4.1



This is a randomized (1:1), single center, placebo-controlled, double blind crossover phase II study. The primary objective is to compare the proportion of patients who have an increase in pain score of ≥3 from baseline in cycle 1 between Arm A (pregabalin) and Arm B (placebo). In consultation with the treating physician, the PI will determine what day pegfilgrastim will be initiated in each eligible, consented patient. Pregabalin or placebo will begin on the day chemotherapy is adminstered, and continue for 10 days, with an increase in pregabalin or placebo dose after 4 days. Also see the Treatment Plan example at the front of this protocol for a graphic of dosing of study medication, chemotherapy and pegfilgrastim during a given chemotherapy cycle in a breast

cancer patient receiving chemotherapy.

Pregabalin/Placebo Treatment Dosage and Administration:

4.3 Pregabalin or matching placebo will be administered at 75 mg BID for 4 days, to patients receiving pegfilgrastim for hematologic malignancies or breast cancer patients on myelosuppressive chemotherapy. Starting on the fifth day (after the 4 days at 75mg), the dose of study medication will be increased to 150 mg PO BID provided the patient is tolerating the lower dose (ie, they are not experiencing any pregabalin associated toxicities > Grade 1). This will be determined by the research team on the day of pegfilgrastim administration. See section 4.7 for additional information.

At the time of consent and randomization, patients will be given two bottles of study medication, one labeled for cycle 1 and one for cycle 2. They will be instructed on the specific date to initiate their first dose of study medication for each cycle, to start on the day of chemotherapy.

Assessment of Efficacy:

6.3 Any patient who receives all pregabalin/matching placebo doses during the 4 day titration period in cycle 1 will be evaluable for any efficacy objective concerning cycle 1. Any patient who also receives all pregabalin/matching placebo doses during the 4 day titration period in cycle 2 will be evaluable for efficacy objectives across the 2 cycles.

Time and Events Table:
6.1

			Cycle 1 & Cycle 2					
	Screening	**Randomization**	**Day of Chemotherapy**	**Chemotherapy**	**Pegfilgrastim 6mg SC x1 dose; dose scheduled in relation to chemotherapy in consultation with MD**	**Day of Pegfilgrastim**	**Phone Call #1 after Pegfilgrastim**	**Phone Call #2 after Pegfilgrastim**
Informed consent	X							
Confirm lack of bone metastases	X							
Review of concomitant medication	X							
Pregnancy test	X							
Serum creatinine	X							
Pregabalin/Placebo			X			Continue study medication for 7 days starting from the day of pegfilgrastim		
10 point numerical pain scale & log	X					Patient maintains log of pain and pain medications for 7 days starting from the day of pegfilgrastim		
Patient adherence log	Provide		Patient begins diary of pregabalin			Patient continues diary of pregabalin		
ID pain scale	X						X	X
Toxicity monitoring				X	X	X	X	X

LCCC 1314: A phase II, placebo-controlled, double-blind, randomized crossover trial of pregabalin for the prophylaxis of pegfilgrastim-induced bone pain

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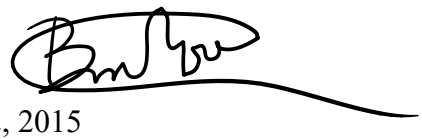
Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name: Benyam Muluneh, PharmD, BCOP, CPP

PI Signature: 

Date: April 12, 2015

TREATMENT PLAN EXAMPLE FOR BREAST CANCER PATIENT
-see schema for full study design

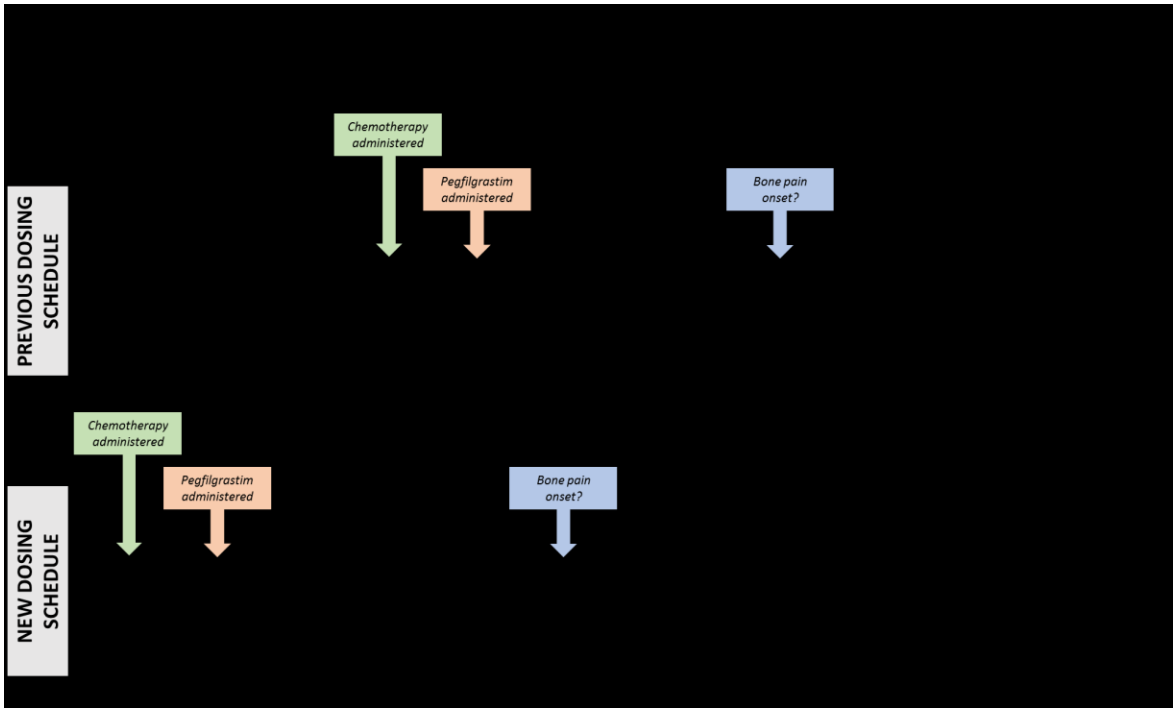


TABLE OF CONTENTS

1.0 BACKGROUND AND RATIONALE 4

1.1 Study Synopsis 4

1.2 Pegfilgrastim-associated Bone Pain 4

1.3 Pregabalin....5

1.4 Study Design 6

1.5 Rationale....8

2.0 STUDY OBJECTIVES....8

2.1 Primary Objective 8

2.2 Secondary Objectives....8

2.3 Exploratory Objective 9

2.4 Primary Endpoint 9

2.5 Secondary/Exploratory Endpoints 9

3.0 PATIENT ELIGIBILITY 10

3.1 Inclusion Criteria....10

3.2 Exclusion Criteria....11

4.0 TREATMENT PLAN....12

4.1 Schema 12

4.2 Treatment Assignment and Blinding....12

4.3 Pregabalin/Placebo Treatment Dosage and Administration....13

4.4 Pegfilgrastim Dosage and Administration 13

4.5 Pain Measures 14

4.6 Patient Phone Contact 14

4.7 Pregabalin Toxicities and Dosing Delays/Dose Modifications....14

4.8 Concomitant Medications/Treatments....15

4.9 Duration of Pregabalin/Matching Placebo Therapy....16

4.10 Duration of Follow Up....16

4.11 Removal of Patients from Protocol Therapy....16

4.12 Study Withdrawal....16

5.0 PREGABALIN DRUG INFORMATION....17

5.1 Dosage and Administration....17

5.2 Storage and Handling....17

5.3 Adverse Events....17

6.0 EVALUATIONS AND ASSESSMENTS....21

6.1 Time and Events Table....21

6.2 Footnotes for Time and Events Table....22

6.3 Assessment of Efficacy....22

6.4 Assessment of Safety....22

7.0 ADVERSE EVENTS....23

7.1 Definitions....23

7.2 Documentation of non-serious AEs or SARs....24

7.3 SAEs or Serious SARs....25

7.4 Data and Safety Monitoring Plan....26

8.0 STATISTICAL CONSIDERATIONS....27

8.1 Study Design and Accrual....27

8.2 Sample Size and Stopping Rule....27

8.3 Data Analysis Plans....28

9.0 STUDY MANAGEMENT 29

9.1 Institutional Review Board (IRB) Approval and Consent 29

9.2 Required Documentation 29

9.3 Registration Procedures 30

9.4 Data Management and Monitoring/Auditing 30

9.5 Adherence to the Protocol 30

9.6 Amendments to the Protocol 31

9.7 Record Retention 32

9.8 Obligations of Investigators 32

10.0 REFERENCES 33

11.0 APPENDICES 34

11.1 Appendix 1: Numerical Scale for Pain[6]: 34

11.2 Appendix 2: Neuropathic Pain Scale (ID Pain)[7]: 34

11.3 Appendix 3: Model Patient Pain Monitoring Log 35

11.4 Appendix 4: Model Pregabalin/Placebo Medication Compliance Diary 36

1.0 BACKGROUND AND RATIONALE

1.1 Study Synopsis

This is a randomized, double-blind, placebo-controlled, single center, crossover phase II clinical trial investigating the prophylactic analgesic effects of pregabalin (Lyrica®) during the first two cycles of chemotherapy in cancer patients receiving pegfilgrastim (Neulasta®). We have restricted enrollment in this trial to breast cancer patients and those with hematological malignancies, who require pegfilgrastim prophylactically. Pegfilgrastim is associated with bone pain (which can be severe) when used in these populations.

In this study 60 patients are randomized to Arm A (pregabalin in cycle 1; placebo in cycle 2) or Arm B (placebo in cycle 1; pregabalin in cycle 2). The primary objective is to compare the proportion of patients who have an increase in pain score of ≥3 from baseline through the end of study medication in cycle 1 between Arm A (pregabalin) and Arm B (placebo).

A secondary objective is to compare of the proportion of patients with an increase in pain score of ≥3 from baseline between pregabalin and placebo across the 2 cycles. Other outcomes evaluated are the safety of this combination, the proportion of patients with an increase in bone/joint pain score of ≥3 from baseline, the proportion of patients with severe pain, the maximum change in pain score, and time to and number of days of rescue (breakthrough) analgesics.

For measuring pain, we will rely on a validated 10-point numerical pain scale that patients will complete prior to initiation of pregabalin in each cycle, and for 7 days starting the day of pegfilgrastim administration in each cycle.

1.2 Pegfilgrastim-associated Bone Pain

Pegfilgrastim is a pegylated form of granulocyte colony-stimulating factor (G-CSF) which is FDA approved to decrease the duration of neutropenia, thus the incidence of infection, by stimulating granulocyte production in patients receiving myelosuppressive chemotherapy associated with a significant risk of febrile neutropenia.[1] As a long-acting product, this pegylated version is administered once per chemotherapy cycle, 24-72 hours after chemotherapy is complete.

Bone and skeletal pain due to pegfilgrastim have been reported in early clinical trials at rates of 22-33%, with sites of pain commonly noted in the lower back, posterior iliac crest and sternum. However more recent studies have found incidences as high as 59-71% with 27% experiencing severe pain (pain greater than 5 on a 10-point scale).[2,3] Notably, Kirshner and colleagues conducted a phase III randomized trial evaluating the non-steroidal anti-inflammatory (NSAID) naproxen for the prevention of pegfilgrastim-related bone pain in patients with nonmyeloid cancer. Patients completed questionnaires at home documenting any new bone or joint pain post pegfilgrastim. The majority

enrolled (68%) had breast cancer, and 7% had hematological malignancies. In this study of 510 patients, (257 on naproxen and 253 on placebo), the overall pain incidence was 71.3% (27% severe) in the placebo group and 61.1 % (19.2% severe) in the naproxen group. While naproxen significantly reduced the incidence of all and severe bone pain, and reduced the duration of bone pain (from 2.4 to 1.9 days), the authors concluded that novel preventive strategies are needed given the high incidence of bone pain even when naproxen is used for treatment.[3]

The average onset of bone pain is 4 days after initiation of pegfilgrastim and with a duration of between 2-3 consecutive days.[3,4] Because patients get multiple cycles of chemotherapy every 14-28 days, these repeated episodes of bone pain can significantly hinder quality of life. In the case where pegfilgrastim is withheld because of severe bone pain, chemotherapy dose-intensity and schedule often cannot be maintained threatening efficacy in addition to an increased potential for infectious complications.

Bone pain secondary to pegfilgrastim is usually treated with NSAIDs such as ibuprofen or naproxen, or opioids. Opioids are often preferred over NSAIDs because patients may be thrombocytopenic and at risk for gastrointestinal bleeding, and NSAIDs increase the risk of both of these adverse events. In addition, NSAIDs have an antipyretic property which is problematic in neutropenic patients. Their use can mask febrile neutropenia, which could mean an important sign of infection is missed in immunocompromised hosts. Because there are no established predictive factors for development of bone pain[3], nearly all patients who get pegfilgrastim receive a prescription for opioids in case they experience pain. Patients do not take pain medications to prevent the pain, but instead generally wait until they experience pain before starting these analgesics. In general, pain is more difficult to control once it has started, thus a prophylactic strategy may be more advantageous. To avoid any impact on the dose and/or schedule of chemotherapy, it would be optimal to prevent bone pain occurring after administration of pegfilgrastim, rather than advising the patient to treat this pain if/when it happens.

1.3 Pregabalin

1.3.1 Introduction

Pregabalin (Lyrica®) is a medication indicated for various types of nerve-related pain, and as an adjunctive therapy for patients with partial onset seizures. It binds to the alpha$_2$-delta subunit of the voltage gated calcium channels within the central nervous system (CNS) and inhibits excitatory neurotransmitter release. Pregabalin is structurally related to gamma-aminobutyric acid (GABA) but does not bind to GABA or benzodiazepine receptors. Pregabalin's maximal analgesic onset of action is about one week. Plasma levels of pregabalin peak in 1.5 hours (3 hours with food), and it has an elimination half-life of approximately 6 hours. Significant drug-drug interactions are not associated with pregabalin as it

undergoes negligible metabolism prior to excretion in the urine, and does not bind to serum proteins.

1.3.2 Safety

Common toxicities associated with pregabalin include peripheral edema (≤16%), CNS effects (such as dizziness [8-45%], somnolence [4-36%], ataxia [1-20%], headache [5-15%], fatigue [5-11%]) and weight gain (≤16%). Rare but serious toxicities associated with pregabalin include angioedema, hypersensitivity, thrombocytopenia, rhabdomyolysis, suicidal ideation, and visual disturbances. Pregabalin-induced adverse effects are likely to be more prominent when administered continuously long-term for chronic conditions versus intermittent use with a regimen of chemotherapy. The rates of drug discontinuation due to toxicity in pregabalin placebo-controlled registrational trials were: 3-11% for pregabalin daily-dose of 150 mg, 16% for pregabalin daily-dose of 300 mg and and 5-10% for placebo.[5]

No known drug-interaction exists between pregabalin and pegfilgrastim, and based on their mechanisms of action and pharmacokinetics, none is predicted. Based on experience of the investigators of this trial, the two drugs are often used in combination in cancer patients with no adverse outcomes.

Dose-dependent increases in the incidence of hemangiosarcoma were reported in mice that received pregabalin at doses of 200-500 mg/kg for two years. The lowest dose and AUC that correlated with the incidence of hemangiosarcomas was estimated to be at an equivalent human dose of 600 mg per day. Of note, there have never been any reported cases of carcinogenicity with pregabalin and it is considered safe and often utilized for the management of neuropathic pain in cancer patients.

Pregabalin can also rarely cause a modest decrease in platelet counts with an average drop of 20 x $10^3/\mu L$ as compared to 11 x $10^3/\mu L$ in the placebo arm from registrational clinical trials (pregabalin prescribing information). Clinically significant decreased platelet counts (defined as 20% below baseline value and $<150 \times 10^3/\mu L$) occurred in 3% of pregabalin-treated patients (compared to 2% in the placebo group). We do not anticipate this will be an issue with LCCC1314 as pregabalin administration will be limited to 11 days duration during either cycle 1 or cycle 2. Further, in subjects enrolled with hematological malignancies, any effects on platelets from pregabalin will be dwarfed by those from the chemotherapy regimens this group receives, and we do not anticipate pregabalin will delay the time to recovery. In addition, platelet counts will be obtained regularly as part of the post-chemotherapy standard of care.

1.4 Study Design

This is a randomized, double-blind, placebo-controlled, crossover phase II clinical trial of 60 patients investigating the prophylactic analgesic effects of pregabalin (Lyrica®) during the first two cycles of chemotherapy in cancer patients receiving

pegfilgrastim (Neulasta®). We have restricted enrollment in this trial to breast cancer patients and those with hematological malignancies, who require pegfilgrastim prophylactically. This allows us to limit the variety of tumor types enrolled, and to restrict our analysis to pegfilgrastim, versus filgrastim.

Similar to Kirshner[3], we will not exclude patients who are receiving analgesics at the time of enrollment, but the type and doses of each at the time of screening will be recorded. Patients who are enrolled and subsequently require an increase in analgesics due to the discomfort associated with placement of a chemotherapy port will be withdrawn from the study if they still require these analgesics on day 1 (D1) of chemotherapy. The use of acetaminophen for blood transfusions will be allowed, with the dose and frequency documented.

The primary objective of the trial will focus on cycle 1. Using a crossover component may increase the rate of accrual and will give us more power to detect potential differences in pain measures between pregabalin and placebo. However, given that pegfilgrastim's association with bone pain varies between cycles 1 and 2, and given the possibility of increased analgesic use in the placebo group in cycle 1, evaluation of the data across 2 cycles will be secondary, and hypothesis generating.

1.4.1 Focus on Cycle 1

The oncology literature supports increased frequency of bone pain when pegfilgrastim is used in cycle 1 of chemotherapy compared to subsequent cycles.[8] In a retrospective review of 7 randomized controlled trials comparing filgrastim to pegfilgrastim, the incidence of bone pain was most common in the first cycle (46.2% for pegfilgrastim) of chemotherapy, decreasing in subsequent cycles (30.9% in cycle 2). Within the same study, the authors performed an exploratory analysis of 23 chemotherapy-induced neutropenia trials that incorporated pegfilgrastim. Within this group of studies, the incidence of bone pain decreased from 35.1% (cycle 1) to 22.7% (cycle 2).[8] Focusing our primary objective on cycle 1 should provide the best opportunity to compare the incidence of pain between pregabalin and placebo when using pregabalin as a prophylactic.

We chose a change in pain score of ≥3 since this change is considered clinically meaningful by the research team based on clinical experience.

1.4.2 Schedule and Dose of Pregabalin

Because we are interested in the prevention of pain, the duration of treatment with pregabalin for less than one week prior to pegfilgrastim with continued dosing for 10 days starting from the day of pegfilgrastim administration will be sufficient for primary prophylaxis. See the Treatment Plan example at the front of this protocol for a graphic of dosing of study medication, chemotherapy and pegfilgrastim during a given chemotherapy cycle in a breast cancer patient receiving chemotherapy.

The analgesic effect of pregabalin is dose-responsive often exerting its effect at an average oral dose of 150 mg BID. For all approved indications of pregabalin, patients are generally started at a lower dose (e.g., 75 mg BID), with the dose increased to 150 mg BID to improve tolerance. Therefore, we will start all patients on 75 mg PO BID to begin on the day of chemotherapy prior to increasing the dose to 150 mg PO BID provided the patient is not experiencing >grade 1 pregabalin-associated side effects.

Given the short half-life of pregabalin, the schedule of administration as outlined in the schema allows a sufficient washout period between cycle 1 and initiation of study medication prior to cycle 2.

1.4.3 Early Stopping Rule

In this trial toxicity will be monitored continuously, with an early stopping rule for cycle 1 in place to avoid excess toxicity related to use of this prophylactic analgesic. The early stopping rule, applied to each arm separately, is based on a maximum acceptable ≥ grade 2 pregabalin-associated toxicity rate of 25%. Pregabalin associated toxicities not included in this rate of 25% are weight gain or dry mouth. In assessing adverse events and attribution during the course of this study, we will consider those adverse events commonly associated with pregabalin, the specific chemotherapy administered and pegfilgrastim.

1.5 Rationale

The purpose of this study is to evaluate the preventative effects of pregabalin on pegfilgrastim-induced bone pain in cycle 1. Because G-CSF receptors are found at nerve endings which modulate the pain signal, blocking this with pregabalin is theorized to prevent the occurrence of this adverse effect.[9]

If the data suggest a role for pregabalin as a prophylactic analgesic in this setting, data generated from the primary objective along with the additional data collected from the crossover portion will be used to design a larger, multicenter study.

2.0 STUDY OBJECTIVES

2.1 Primary Objective

2.1.1 Compare the proportion of patients who have an increase in pain score of ≥ 3 from baseline through the end of study medication in cycle 1 between Arm A and Arm B

2.2 Secondary Objectives

2.2.1 Compare the proportion of patients who have an increase in pain score of ≥ 3 from baseline between pregabalin and placebo across the 2 cycles

2.2.2 Compare the proportion of patients who have an increase in bone/joint pain score of ≥ 3 from baseline through the end of study medication in cycle 1 between Arm A and Arm B

2.2.3 Compare the number of days of breakthrough analgesic use between pregabalin and placebo within cycle 1 and across the 2 cycles

2.2.4 Compare the proportion of patients with severe pain between pregabalin and placebo within cycle 1 and across the 2 cycles

2.2.5 Compare the maximum change in pain score from baseline between pregabalin and placebo within cycle 1 and across the 2 cycles

2.2.6 Compare the maximum neuropathic pain score between pregabalin and placebo within cycle 1 and across the 2 cycles

2.2.7 Describe the safety (assessed via NCI CTCAE v4) of pregabalin when used in the prevention of bone pain secondary to pegfilgrastim

2.3 Exploratory Objective

2.3.1 Compare pain measures between pregabalin and placebo in the breast cancer and hematological malignancy subgroups separately within cycle 1 and across the 2 cycles

2.3.2 Compare the time to first breakthrough analgesic use between pregabalin and placebo during cycle 1

2.4 Primary Endpoint

2.4.1 Pain score is based on a 10-point numerical scale (see section 11.1) for pain as documented at baseline (at screening for cycle 1 and day 1 of study medication prior to cycle 2) and on patient log (see section 11.3) for 7 days starting the day of pegfilgrastim administration

2.5 Secondary/Exploratory Endpoints

2.5.1 Bone/joint pain score is based on a 10-point numerical scale (see section 11.1) for pain as documented at baseline (at screening for cycle 1 and day 1 of study medication prior to cycle 2) and on patient log (see section 11.3) for 7 days starting the day of pegfilgrastim administration

2.5.2 Severe pain will be measured using the 10-point numerical scale for pain (see section 11.1) as documented on the patient log (section 11.3; severe pain is defined as a score >5 on this scale, similar to Kirshner and colleagues[3])

2.5.3 A day of breakthrough analgesic use is defined as any day in which patient increases the dose of any pain medication compared to baseline, or the addition of a new pain medication as documented on patient log (see section 11.3); time to first breakthrough analgesic use is defined as the time in days from pegfilgrastim administration to the first day patient uses breakthrough analgesic

2.5.4 Neuropathic pain is assessed via the Neuropathic Pain Scale (see section 11.2) as documented from phone calls twice during study medication administration post pegfilgrastim administration.

3.0 PATIENT ELIGIBILITY

3.1 Inclusion Criteria

Subject must meet all of the inclusion criteria to participate in this study:

3.1.1 Age ≥18 years

3.1.2 Diagnosis of a non-myeloid hematologic malignancy scheduled to initiate a cycle of chemotherapy that requires prophylactic use of a granulocyte colony-stimulating growth factor (based on the provider's discretion), provided the schedule of chemotherapy cycles allows the use of pegfilgrastim at a dose of 6 mg SC once per cycle

OR

Diagnosis of breast cancer scheduled to initiate dose-dense doxorubicin and cyclophosphamide (AC) chemotherapy or docetaxel and cyclophosphamide (TC) chemotherapy that requires prophylactic use of a granulocyte colony-stimulating growth factor, provided the schedule of chemotherapy cycles allows the use of pegfilgrastim, at a dose of 6 mg SC once per cycle; pegfilgrastim scheduled for 24 hours post chemotherapy.

3.1.3 Schedule of chemotherapy and pegfilgrastim initiation can accommodate initiation of pregabalin 4 days prior to pegfilgrastim dose

3.1.4 Baseline pain scores <7 as measured via 10-point numerical scale for pain (see section 11.1); pain score and use of any non-opioid pain medication must be self-reported as stable (same dose and frequency) over the 7 days prior to screening; for opioids, patient must self-report the same dose and frequency over the 28 days prior to screening. Patients who are receiving peri-procedural short-acting analgesics will still be included as long as they are no longer receiving analgesics by D1 of chemotherapy.

3.2 Exclusion Criteria

Any subject meeting any of the following exclusion criteria at baseline will be ineligible for study participation:

3.2.1 A history of (within one month) or current pregabalin use

3.2.2 Baseline pain scores ≥7 as measured via 10-point numerical scale for pain (see section 11.1)

3.2.3 Unwilling to discontinue use of antihistamines from 7 days prior to D1 of study medication

3.2.4 CrCl ≤60 ml/min (as measured via Cockcroft-Gault) based on serum creatinine measured as part of standard of care prior to administration of chemotherapy

3.2.5 Women of childbearing potential must have a negative serum pregnancy test prior to initiating therapy (note, this test should be standard of care prior to administration of chemotherapy)

3.2.6 Patient is unable or unwilling to abide by the study protocol or cooperate fully with the investigator

3.2.7 Eligible and agrees to enroll into therapeutic trial ongoing at LCCC (i.e., the treatment trial will take precedence over LCCC1314)

3.2.8 Currently receiving therapeutic doses of anticoagulants (ie, prophylactic use of anticoagulants is allowed) due to possibility of dizziness and falls while on pregabalin

3.2.9 Currently receiving aromatase inhibitors or agents targeted against Ph+ leukemias (i.e., imatinib, dasatinib, nilotinib, nolotinib, and ponatinib) or scheduled to start these drugs during cycle 1 of scheduled chemotherapy.

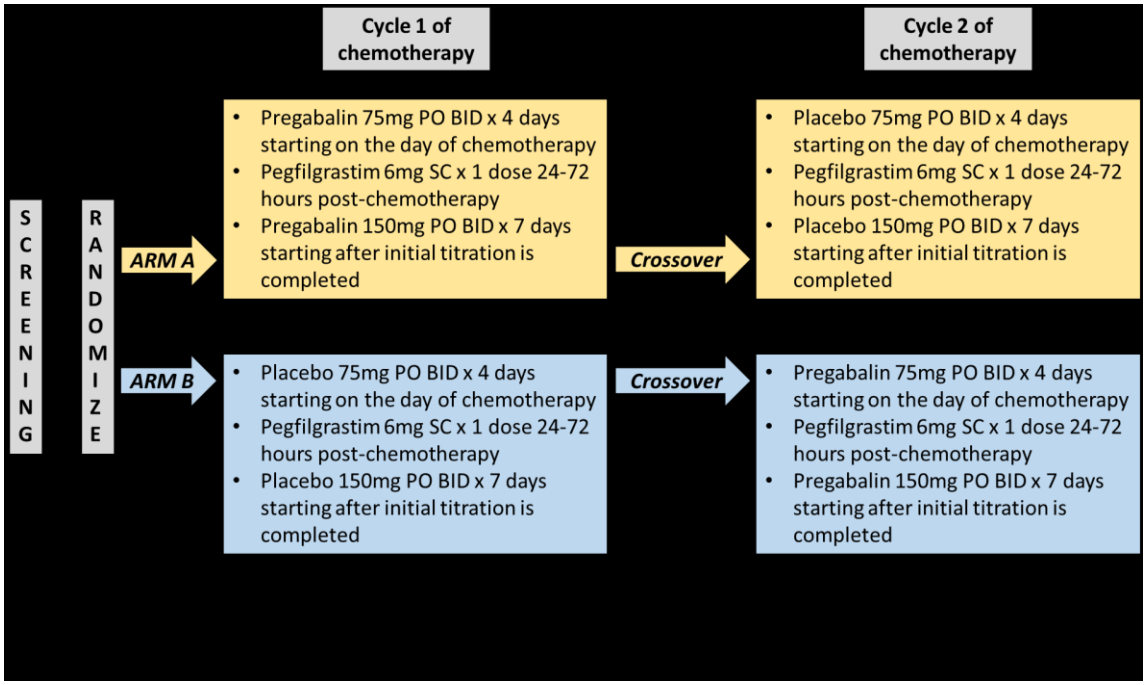
3.2.10 Presence of bone metastases

3.2.11 History of angioedema

3.2.12 History of a seizure disorder

4.0 TREATMENT PLAN

4.1 Schema



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4.2 Treatment Assignment and Blinding

At the end of the screening period, eligible patients will be randomly assigned in a 1:1 ratio to Arm A or Arm B in a double-blind fashion such that neither the Investigator, Sponsor, nor the patient will know which agent is being administered. The randomization will be assigned by the statistician(s) of record who will provide this information to UNC Investigational Drug Services. A block randomization scheme will be utilized, and stratified by tumor type (breast cancer or hematological malignancy) and age (<65 or ≥65). Anecdotally, younger patients seem to self-report pain more frequently than older patients. Stratification by age ensures some comparability between arms related to this factor.

Pregabalin and placebo will be identical in appearance in order to preserve blinding.

4.2.1 Emergency Unblinding

Unblinding may occur for emergency purposes only. Investigators should note that the occurrence of a SAE should not routinely precipitate the immediate unblinding of the label. Patients will be unblinded as per the Unblinding Plan, a document provided separate to this protocol.

4.3 Pregabalin/Placebo Treatment Dosage and Administration

Pregabalin or matching placebo will be administered at 75 mg BID for 4 days, to patients receiving pegfilgrastim for hematologic malignancies or breast cancer patients on myelosuppressive chemotherapy. Starting on the fifth day of pegfilgastim (after the 4 days at 75 mg), the dose of study medication will be increased to 150 mg PO BID provided the patient is tolerating the lower dose (ie, they are not experiencing any pregabalin associated toxicities >Grade 1). This will be determined by the research team on the day of pegfilgrastim administration. See section 4.7 for additional information.

At the time of consent and randomization, patients will be given two bottles of study medication, one labeled for cycle 1 and one for cycle 2. They will be instructed on the specific date to initiate their first dose of study medication for each cycle, to start on the day of chemotherapy.

Patients will be instructed to document their adherence by noting the time of each dose on a diary (see section 11.4 for model diary) and to take their first daily dose of pregabalin at approximately the same time each day. The second dose of pregabalin should be administered approximately 12 hours after the morning dose. If a dose is vomited or if a dose is missed for any reason, the dose should not be made up. Patients should note any missed doses on their medication diary, see section 11.4.

Pregabalin/matching placebo may be taken with or without a meal; tablets should be swallowed whole with a glass of water, and should not be chewed or crushed.

4.4 Pegfilgrastim Dosage and Administration

Pegfilgrastim 6 mg SC is to be administered as per standard of care based on the judgment of the prescribing hematologist/oncologist. It is being provided free of charge to study participants by Amgen. The date of administration of pegfilgrastim in relation to the chemotherapy regimen will be decided by the hematologist/oncologist. For hematologic malignancy patients, pegfilgrastim is usually administered 24 to 72 hours after chemotherapy. For breast cancer patients receiving dose dense AC or receiving TC, pegfilgrastim is usually administered 24 hours after chemotherapy. See sections 7.2 and 7.4.3 regarding

required documentation and reporting of any safety issues (other than adverse events) associated with the pegfilgrastim product or its administration.

4.5 Pain Measures

4.5.1 Ten-point numerical scale

The ten-point numerical scale is scored from 0 to 10. Patients will complete this scale at screening, and then on a daily basis for 7 days starting the day of pegfilgrastim administration in both cycles 1 and 2. They will use this scale to rate their pain (and separately bone/joint pain) with 0 signifying "no pain" and 10 signifying "the worst pain you can imagine." See section 11.1 and section 11.3 for the model patient pain monitoring log.

4.5.2 ID-Pain (Neuropathic Pain Scale)

The ID-Pain scale is a 6-item, patient-completed screening tool designed to help differentiate nociceptive and neuropathic pain. Details of the scale and scoring are located in section 11.2. Patients will complete this scale on the day of enrollment, and then will be asked the questions from this scale by the research team via telephone twice during study medication administration after pegfilgrastim administration in cycles 1 and 2.

4.6 Patient Phone Contact

Patients will be contacted by a study team member twice during study medication administration after pegfilgrastim administration in cycles 1 and 2. Patients will be asked about any side effects they may be experiencing from their study medication. If the patient makes any mention of pain, the study coordinator will remind the patient to note this information using the pain logs. Patients will also be reminded during these phone calls to complete the daily pain log and compliance diary (see 11.3 and 11.4 for model pain monitoring log and model medication compliance diary) and will be asked the questions from the Neuropathic Pain Scale (see 11.2) by the research team. Patients will also be reminded to complete the list and doses of each pain medication on the day they start their pre-cycle 2 study medication.

4.7 Pregabalin Toxicities and Dosing Delays/Dose Modifications

Any patient who receives at least one dose of pregabalin/matching placebo on this protocol will be evaluable for toxicity. Each patient will be assessed regularly for the development of any toxicity according to the Time and Events tables (see Section 6.0). Toxicity will be assessed according to the NCI CTCAE, v4.

In assessing adverse events and attribution during the course of this study, we will consider those adverse events commonly associated with pregabalin, the specific chemotherapy administered and pegfilgrastim.

The most common adverse reactions in placebo controlled trials of pregabalin (≥5% and twice the frequency of placebo) include dizziness, somnolence, dry

mouth, edema, blurred vision, weight gain, and difficult with concentration/ attention. For complete prescribing information, see www.pfizer.com. See section 5.3 for additional information on pregabalin warnings and precautions.

There have been postmarketing reports of hypersensitivity in patients shortly after initiation of treatment with pregabalin. Adverse reactions included skin redness, blisters, hives, rash, dyspnea, and wheezing. Discontinue pregabalin immediately in patients with these symptoms.

In clinical trials, dizziness and somnolence generally began shortly after the initiation of pregabalin therapy and occurred more frequently at higher doses.

If a patient experiences ≤grade 1 pregabalin associated toxicity, the patient should remain on the same dose of pregabalin/matching placebo, and be monitored daily via telephone contact until the side effect is resolved. If a patient experiences grade ≥2 pregabalin associated toxicity, the dose can be reduced to 75 mg PO BID if they are receiving 150 mg PO BID. Otherwise, study medication should be permanently discontinued and he/she should be followed up per protocol. See section 5.3 for specific information on pregabalin related adverse events. See section 8.2 for details on the continuous toxicity monitoring for the study and early stopping rule.

If the CrCl ≤60 ml/min at the start of cycle 2, then the patient should be withdrawn from study medication and followed up per protocol.

4.8 Concomitant Medications/Treatments

4.8.1 Prohibited Medications

Aromatase inhibitors and agents targeted against Ph+ leukemias (i.e., imatinib, dasatinib, nilotinib, nolotinib, and ponatinib) are prohibited as joint pain, stiffness and arthralgia are common side effects associated with this class of drugs. Antihistamines will also be prohibited as there is anecdotal evidence of analgesic effects from this class of drugs against growth-factor induced bone pain.

4.8.2 Drug Interactions

Pregabalin is predominantly excreted unchanged in the urine, undergoes negligible metabolism in humans (<2% of a dose recovered in urine as metabolites), and does not bind to plasma proteins. Therefore its pharmacokinetics is unlikely to be affected by other agents through metabolic interactions or protein binding displacement. *In vitro* and *in vivo* studies showed that pregabalin is unlikely to be involved in significant pharmacokinetic drug interactions.

No known drug-interaction exists between pregabalin and pegfilgrastim, and based on their mechanisms of action and pharmacokinetics, none is predicted.

Based on experience of the investigators of this trial, the two drugs are often used in combination in cancer patients with no adverse outcomes.

4.9 Duration of Pregabalin/Matching Placebo Therapy

Treatment with pregabalin/matching placebo may continue until:

- Patient continues to require pain medication related to port placement on D1 of chemotherapy
- CrCl ≤60 ml/min at start of cycle 2
- Patient has completed 11 days of pregabalin/matching placebo therapy during cycle 2
- Intercurrent illness prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from treatment, **OR**
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator

4.10 Duration of Follow Up

All enrolled patients for pregabalin prophylaxis will be followed up per protocol through the last day of pregabalin/placebo administration in cycle 2. Patients removed from study treatment for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

4.11 Removal of Patients from Protocol Therapy

Patients will be removed from study treatment when any of the criteria listed in section 4.9 apply. Notify the Principal Investigator, and document the reason for removal from study treatment and the date the patient was removed in the Case Report Form (CRF). The patient should be followed-up per protocol.

In case a patient decides to prematurely discontinue protocol therapy ("refuses treatment"), the patient should be asked if she or he may still be contacted for further scheduled study assessments. The outcome of that discussion should be documented in both the medical records and in the CRF.

Excessive patient withdrawals from protocol therapy or from the study can render the study un-interpretable; therefore, unnecessary withdrawal of patients should be avoided.

4.12 Study Withdrawal

If a patient decides to withdraw from the study (and not just from protocol therapy) all efforts should be made to complete and report study assessments as thoroughly as possible. The investigator should contact the patient or a responsible relative by telephone or through a personal visit to establish as completely as possible the reason for the study withdrawal. A complete final evaluation at the time of the patient's study withdrawal should be made with an

explanation of why the patient is withdrawing from the study. If the reason for removal of a patient from the study is an adverse event, the principal specific event will be recorded on the CRF

5.0 PREGABALIN DRUG INFORMATION

See www.pfizer.com for the complete pregabalin prescribing information.

5.1 Dosage and Administration

See section 4.3 for the doses to be used in the current study LCCC1314. For its approved indications, the starting and optimal doses are listed in the table below.

Indication	Starting Dose	Optimal Dose
Diabetic Peripheral Neuropathy	50 mg TID	100 mg TID
Postherpetic Neuralgia	75 mg BID	150 mg BID
Partial Onset Seizures	75 mg BID or 50 mg TID	Titrate to efficacy and tolerability to maximum of 600 mg daily
Fibromyalgia	75 mg BID	300-450 mg daily

5.1.1 Patients with Renal Impairment

In view of dose-dependent adverse reactions and since pregabalin is eliminated primarily by renal excretion, dose is adjusted in patients with reduced renal function. In this study patients with impaired renal function (defined as CrCL ≤ 60 mL/min) will be excluded.

5.2 Storage and Handling

Recommended storage is at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) per package insert recommendations.

5.3 Adverse Events

In addition to the safety information in section 1.3 and below, see the prescribing information at www.pfizer.com for detailed safety information. Most common adverse reactions (≥ 5% and twice placebo) from registrational trials were dizziness, somnolence, dry mouth, edema, blurred vision, weight gain and abnormal thinking (primarily difficulty with concentration/attention). In addition to its tumorigenic potential and its association with decreased platelet counts described in section 1.3, additional warnings and precautions related to the following are in the pregabalin prescribing information.

5.3.1 Angioedema

There have been postmarketing reports of angioedema in patients during initial and chronic treatment with pregabalin. Specific symptoms included swelling of the face, mouth (tongue, lips, and gums), and neck (throat and larynx). There were reports of life-threatening angioedema with respiratory compromise requiring

emergency treatment. Discontinue pregabalin immediately in patients with these symptoms.

Exercise caution when prescribing pregabalin to patients who have had a previous episode of angioedema. In addition, patients who are taking other drugs associated with angioedema (e.g.,angiotensin converting enzyme inhibitors [ACE-inhibitors]) may be at increased risk of developing angioedema.

5.3.2 Hypersensitivity

There have been postmarketing reports of hypersensitivity in patients shortly after initiation of treatment with pregabalin. Adverse reactions included skin redness, blisters, hives, rash, dyspnea, and wheezing. Discontinue pregabalin immediately in patients with these symptoms.

5.3.3 Withdrawal of Antiepileptic Drugs (AEDs)

As with all AEDs, if pregabalin is withdrawn abruptly or rapidly in patients with seizure disorders, there is a potential for increased seizure frequency. When used as an anti-seizure medication or in patients with a history of seizures, pregabalin should be withdrawn gradually over a minimum of 1 week.

5.3.4 Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including pregabalin, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Monitor patients treated with any AED for any indication for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated. Patients should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. These behaviors should be immediately reported to healthcare providers.

5.3.5 Peripheral Edema

Pregabalin treatment may cause peripheral edema. In short-term trials of patients without clinically significant heart or peripheral vascular disease, there was no apparent association between peripheral edema and cardiovascular complications such as hypertension or congestive heart failure. Peripheral edema was not associated with laboratory changes suggestive of deterioration in renal or hepatic function.

In controlled clinical trials the incidence of peripheral edema was 6% in the pregabalin group compared with 2% in the placebo group. Weight gain was reported in 4% of patients on pregabalin in the overall safety database in studies

of pain associated with diabetic peripheral neuropathy. In this population, the incidence of edema and weight gain is increased when patients are also on a thiazolidinedione class of antidiabetic drugs. As the thiazolidinedione class of antidiabetic drugs can cause weight gain and/or fluid retention, possibly exacerbating or leading to heart failure, exercise caution when co-administering pregabalin and these agents. Because there are limited data on congestive heart failure patients with New York Heart Association (NYHA) Class III or IV cardiac status, exercise caution when using pregabalin in these patients.

5.3.6 Dizziness and Somnolence

Pregabalin may cause dizziness and somnolence. Inform patients that pregabalin-related dizziness and somnolence may impair their ability to perform tasks such as driving or operating machinery.

In the pregabalin controlled trials, dizziness was experienced by 30% of pregabalin-treated patients compared to 8% of placebo-treated patients; somnolence was experienced by 23% of pregabalin treated patients compared to 8% of placebo-treated patients. Dizziness and somnolence generally began shortly after the initiation of pregabalin therapy and occurred more frequently at higher doses. Dizziness and somnolence were the adverse reactions most frequently leading to withdrawal (4% each) from controlled studies. In pregabalin-treated patients reporting these adverse reactions in short-term, controlled studies, dizziness persisted until the last dose in 30% and somnolence persisted until the last dose in 42% of patients.

5.3.7 Weight Gain

Pregabalin treatment may cause weight gain; in controlled clinical trials of up to 14 weeks, a gain of 7% or more over baseline weight was observed in 9% of pregabalin-treated patients and 2% of placebo-treated patients. The pregabalin associated weight gain was related to dose and duration of exposure, but did not appear to be associated with baseline BMI, gender, or age. Weight gain was not limited to patients with edema.

5.3.8 Abrupt or Rapid Discontinuation

Following abrupt or rapid discontinuation of pregabalin, some patients reported symptoms including insomnia, nausea, headache, anxiety, hyperhidrosis, and diarrhea. It should be tapered gradually over a minimum of 1 week rather than discontinuing the drug abruptly. We do not anticipate this to be an issue with the short duration of pregabalin use in this study.

5.3.9 Ophthalmological Effects

In controlled studies, a higher proportion of patients treated with pregabalin reported blurred vision (7%) than did patients treated with placebo (2%), which resolved in a majority of cases with continued dosing. Although the clinical significance of the ophthalmologic findings is unknown, inform patients to

notify their physician if changes in vision occur. If visual disturbance persists, consider further assessment.

5.3.10 Creatine Kinase Elevations

Mean changes in creatine kinase from baseline to the maximum value were 60 U/L for pregabalin-treated patients and 28 U/L for the placebo patients. In all controlled trials across multiple patient populations, 1.5% of patients on pregabalin and 0.7% of placebo patients had a value of creatine kinase at least three times the upper limit of normal. Three pregabalin treated subjects had events reported as rhabdomyolysis in premarketing clinical trials. The relationship between these myopathy events and pregabalin is not completely understood because the cases had documented factors that may have caused or contributed to these events. Instruct patients to promptly report unexplained muscle pain, tenderness, or weakness, particularly if these muscle symptoms are accompanied by malaise or fever. Discontinue treatment with pregabalin if myopathy is diagnosed or suspected or if markedly elevated creatine kinase levels occur.

5.3.11 PR Interval Prolongation

Pregabalin treatment was associated with PR interval prolongation. In analyses of clinical trial ECG data, the mean PR interval increase was 3–6 msec at pregabalin doses ≥300 mg/day. This mean change difference was not associated with an increased risk of PR increase ≥25% from baseline, an increased percentage of subjects with on-treatment PR >200 msec, or an increased risk of adverse reactions of second or third degree AV block.

6.0 EVALUATIONS AND ASSESSMENTS

6.1 Time and Events Table

			Cycle 1 & Cycle 2					
	Screening	**Randomization**	**Day of Chemotherapy**	**Chemotherapy**	**Pegfilgrastim 6mg SC x1 dose; dose scheduled in relation to chemotherapy in consultation with MD**	**Day of Pegfilgrastim**	**Phone Call #1 after Pegfilgrastim**	**Phone Call #2 after Pegfilgrastim**
Informed consent	X							
Confirm lack of bone metastases	X							
Review of concomitant medication	X							
Pregnancy test	X							
Serum creatinine	X							
Pregabalin/Placebo			X			Continue study medication for 7 days starting from the day of pegfilgrastim		
10 point numerical pain scale & log	X					Patient maintains log of pain and pain medications for 7 days starting from the day of pegfilgrastim		
Patient adherence log	Provide		Patient begins diary of pregabalin			Patient continues diary of pregabalin		
ID pain scale	X						X	X
Toxicity monitoring				X	X	X	X	X

6.2 Footnotes for Time and Events Table

1. Twice during study medication administration after pegfilgrastim administration in cycles 1 and 2, a study team member will contact the patient for assessment of neuropathic pain and for pregabalin associated side effects.

2. Confirmation of lack of bone metastases will come from consultation with treating physician. Study subjects will not require any additional testing regarding bone metastases from enrollment into LCCC1314.

3. Serum or urine pregnancy testing should be done per standard of care (SOC) in women of childbearing potential prior to initiating a new cycle of chemotherapy. Results will be documented on the CRF from this SOC test. If this test is not done, the patient will not be eligible for LCCC1314.

4. Serum creatinine should be done per SOC in prior to initiating a new cycle of chemotherapy. Results will be documented on the CRF from this SOC test. If this test is not done, the patient will not be eligible for LCCC1314.

5. See section 11.1.

6. See section 11.3.

7. See section 11.2.

6.3 Assessment of Efficacy

Any patient who receives all pregabalin/matching placebo doses during the 4 day titration period in cycle 1 will be evaluable for any efficacy objective concerning cycle 1. Any patient who also receives all pregabalin/matching placebo doses during the 4 day titration period in cycle 2 will be evaluable for efficacy objectives across the 2 cycles.

6.4 Assessment of Safety

Any patient who receives at least one dose of pregabalin on this protocol will be evaluable for toxicity. Each patient will be assessed regularly for the development of any toxicity according to the Time and Events tables (see Section 6.0). Toxicity will be assessed according to the NCI CTCAE, v 4.

7.0 ADVERSE EVENTS

7.1 Definitions

7.1.1 Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence (e.g., an abnormal laboratory finding, symptom, or disease temporally associated with the use of a drug) in a patient or clinical investigation subject administered a pharmaceutical product and which 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), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) need not be considered AEs and should not be recorded as an AE. Disease progression should not be recorded as an AE, unless it is attributable by the investigator to the study therapy.

7.1.2 Suspected Adverse Reaction (SAR)

A suspected adverse reaction (SAR) is any AE for which there is a *reasonable possibility* that the drug is the cause. *Reasonable possibility* means that there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Causality assessment to a study drug is a medical judgment made in consideration of the following factors: temporal relationship of the AE to study drug exposure, known mechanism of action or side effect profile of study treatment, other recent or concomitant drug exposures, normal clinical course of the disease under investigation, and any other underlying or concurrent medical conditions. Other factors to consider in considering drug as the cause of the AE:

- Single occurrence of an uncommon event known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome)
- One or more occurrences of an event not commonly associated with drug exposure, but otherwise uncommon in the population (e.g., tendon rupture); often more than once occurrence from one or multiple studies would be needed before the sponsor could determine that there is *reasonable possibility* that the drug caused the event.
- An aggregate analysis of specific events observed in a clinical trial that indicates the events occur more frequently in the drug treatment group than in a concurrent or historical control group

7.1.3 Unexpected AE or SAR

An AE or SAR is considered unexpected if the specificity or severity of it is not consistent with the applicable product information (e.g., Investigator's Brochure (IB) for an unapproved investigational product or package insert/summary of product characteristics for an approved product). Unexpected also refers to AEs or SARs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

7.1.4 Serious AE or SAR

An AE or SAR is considered serious if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death;
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- Requires inpatient hospitalization (>24 hours) or prolongation of existing hospitalization;*
- Results in congenital anomaly/birth defect;
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. For reporting purposes, also consider the occurrences of pregnancy as an event which must be reported as an important medical event.

*Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.

Pregnancy that occurs during the study must also be reported as an SAE.

7.2 Other Pegfilgrastim Safety Concerns Associated with a Serious SAR

Other safety concerns in this context means pegfilgrastim product complaints, medication errors, overdose (whether accidental or intentional), misuse, abuse, transmission of infectious agent, or unauthorized use. See section 7.4.3 for information on reporting these concerns to the manufacturer, Amgen, when they are associated with a serious SAR.

7.3 Documentation of non-serious AEs or SARs

For non-serious AEs or SARs, documentation must begin from day 1 of study treatment and continue through the 30 day follow-up period after treatment is discontinued.

Collected information should be recorded in the Case Report Forms (CRF) for that patient. Please include a description of the event, its severity or toxicity grade, onset and resolved dates (if applicable), and the relationship to the study drug. Documentation should occur at least monthly.

7.4 SAEs or Serious SARs

7.4.1 Timing

After informed consent but prior to initiation of study medications, only SAEs caused by a protocol-mandated intervention will be collected (e.g. SAEs related to invasive procedures such as biopsies, medication washout, or no treatment run-in).

For any other experience or condition that meets the definition of an SAE or a serious SAR, recording of the event must begin from day 1 of study treatment and continue through the 30 day follow-up period after treatment is discontinued.

7.4.2 Documentation and Notification

These events (SAEs or Serious SARs) must be recorded for that patient within 24 hours of learning of its occurrence.

7.4.3 Reporting

IRB Reporting Requirements:

UNC:

- UNC will submit an aggregated list of all SAEs to the UNC IRB annually at the time of study renewal according to the UNC IRB policies and procedures.
- The UNC-IRB will be notified of all SAEs that qualify as an Unanticipated Problem as per the UNC IRB Policies using the IRB's web-based reporting system (see section 9.5.3) within 7 days of the Investigator becoming aware of the problem.

Pfizer Reporting Requirements: To ensure patient safety, every SAE, **regardless of suspected causality**, occurring after the patient begins taking study drug and until 4 weeks after the patient has stopped study treatment must be reported to Pfizer within 24 hours of learning of its occurrence. If the event is both a serious SAR and unexpected, the MedWatch 3500A form will be used.

Reports to Pfizer should be faxed to Pfizer U.S. Clinical Trial Department using the Pfizer-provided Reportable Event Fax Cover Sheet at 866-997-8322.

FDA Expedited Reporting requirements for studies conducted under an IND:
If an investigator deems that an event is both a serious SAR AND unexpected, it must be recorded on the MedWatch Form 3500A as per 21 CFR 312.32. The MedWatch 3500a form can be accessed at: http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm. (Please be sure and access form 3500a, and not form 3500). UNC, as the Sponsor of the study, will make the final determination regarding FDA submission.

Once the UNC Principal Investigator determines an event is a serious SAR AND unexpected, the MedWatch 3500A form will be submitted to the FDA.

Amgen Reporting Requirements:
Any safety concerns documented as defined in section 7.2 that are associated with a Serious SAR must be reported to Amgen within one working day of PI awareness.

7.5 Data and Safety Monitoring Plan

The Principal Investigator will provide continuous monitoring of patient safety in this trial with periodic reporting to the Data and Safety Monitoring Committee (DSMC).

Meetings/teleconferences will be held at a frequency dependent on study accrual, and in consultation with the study Biostatistician. These meetings will include the investigators as well as protocol nurses, clinical research associates, regulatory associates, data managers, biostatisticians, and any other relevant personnel the principal investigators may deem appropriate. At these meetings, the research team will discuss all issues relevant to study progress, including enrollment, safety, regulatory, data collection, etc.

The team will produce summaries or minutes of these meetings. These summaries will be available for inspection when requested by any of the regulatory bodies charged with the safety of human subjects and the integrity of data including, but not limited to, the oversight (Office of Human Research Ethics (OHRE) Biomedical IRB, the Oncology Protocol Review Committee (PRC) or the North Carolina TraCS Institute Data and Safety Monitoring Board (DSMB).

The UNC LCCC Data and Safety Monitoring Committee (DSMC) will review the study on a regular (quarterly to annually) basis, with the frequency of review based on risk and complexity as determined by the UNC Protocol Review Committee. The UNC PI will be responsible for submitting the following information for review: 1) safety and accrual data including the number of patients treated; 2) significant developments reported in the literature that may affect the safety of participants or the ethics of the study; 3) preliminary response data; and 4) summaries of team meetings that have occurred since the last report.

Findings of the DSMC review will be disseminated by memo to the UNC PI, PRC, and the UNC IRB and DSMB.

8.0 STATISTICAL CONSIDERATIONS

8.1 Study Design and Accrual

This is a randomized phase II, single center, placebo-controlled, double-blind crossover study. Eligible patients will be randomly assigned in a 1:1 ratio to either Arm A (pregabalin in cycle 1; placebo in cycle 2) or Arm B (placebo in cycle 1; pregabalin in cycle 2). The primary objective is to compare the proportion of patients who have an increase in pain score of ≥3 from baseline through the end of study medication in cycle 1 between Arm A (pregabalin) and Arm B (placebo). Comparisons in pain measures between pregabalin and placebo across the 2 cycles are secondary objectives. See sections 2.4 and 2.5 for the specific definitions of the pain endpoints.

Based on our patient populations and referral patterns, and using the study resources available, we expect to be able to accrue 60 patients meeting the trial eligibility into this single center study within two years. We anticipate that enrolling 60 patients (30 per arm) will ensure 52 evaluable patients.
Using a crossover component may increase the rate of accrual and will give us more power to detect potential differences in pain measures between pregabalin and placebo. However, given that pegfilgrastim's association with bone pain likely varies between cycles 1 and 2, and the possibility of increased analgesic use in the placebo group in cycle 1, evaluation of the data across 2 cycles will be secondary, and hypothesis generating.

8.2 Sample Size and Stopping Rule

The primary objective is to compare the proportion of patients who have an increase in pain score of ≥3 from baseline through the end of study medication in cycle 1 between Arm A (pregabalin) and Arm B (placebo). A Fisher's exact test with a one-sided significance level of 0.05 will have 81% power to detect the difference between a proportion of 0.5 in the placebo group and a proportion of 0.15 in the pregabalin group when the sample size in each group is 26. We plan to enroll 30 patients per arm (60 total) to ensure that we have 26 evaluable patients in each group. Based on clinical experience, it is reasonable to assume that 50% of patients receiving placebo will have an increase in pain score of ≥3. If this percentage was decreased to 15% with the use of pregabalin, this would be considered clinically meaningful. In addition, with 26 evaluable patients per arm, the maximum width of an exact 95% confidence interval will be 0.401. In other words, we will be able to estimate the proportion with a pain score increase of ≥3 within ~20% for each arm.

Sequential boundaries will be used to suspend the trial if excessive toxicity is seen in either arm during cycle 1. If the study reaches a stopping boundary, it may be terminated by the PI, or submitted to the DSMC with a description of the

toxicities and a rationale for why the study should be continued. Toxicities ≥ grade 2 and deemed to be associated with pregabalin in cycle 1 will be counted in the toxicity rate for the purposes of early stopping. The unacceptable toxicities will not include weight gain or dry mouth. The accrual will be halted if the number of patients with toxicities ≥ grade 2 is equal to or exceeds b_n out of n patients who have received at least one dose of pregabalin or placebo and have been monitored for toxicity in cycle 1 (see table below). This is a Pocock type stopping boundary that assumes that a toxicity rate of 0.25 is acceptable, but anything >25% is unacceptable. If the true toxicity rate is equal to 0.25, the probability of crossing the boundary is 0.05.

Stopping Rule for Each Arm

Number of Patients, n	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Boundary, b_n	-	-	-	4	4	5	5	6	6	7	7	7	8	8	9	9	9	10	10	10
Number of Patients, n	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
Boundary, b_n	11	11	11	12	12	12	13	13	14	14										

8.3 Data Analysis Plans

A Fisher's exact test will be used to compare the proportion of patients who have an increase in pain score (overall and specifically bone/joint pain) of ≥3 from baseline through the end of study medication between pregabalin and placebo in cycle 1. The proportion of patients in each arm who have an increase in pain score of ≥3 from baseline through the end of study medication in cycle 1 will also be estimated and reported along with exact 95% confidence intervals. Frequency tables will be used to summarize safety data and any other patient characteristics of interest. Descriptive statistics, including means, standard deviations, medians, and ranges will also be utilized as appropriate.

A Fisher's exact tests will also be used to compare the proportion of patients with severe pain between pregabalin and placebo in cycle 1. The number of days of breakthrough analgesic use, the maximum change in pain score from baseline, and the maximum neuropathic pain score will be compared in cycle 1 between pregabalin and placebo using Wilcoxon Rank Sum tests. Time to first breakthrough analgesic use in cycle 1 will be analyzed using the method of Kaplan and Meier and will be compared between pregabalin and placebo using the log rank test.

Comparisons between pregabalin and placebo across the 2 cycles will be made using standard analysis methods for crossover designs. Specifically, McNemar's

test or the Mainland-Gart test will be used when the outcome is binary (i.e. to compare proportions). The Wilcoxon Rank Sum test on the within patient differences will be used for continuous outcomes. Mixed models may also be considered in this setting.

As an exploratory analysis, and as the sample size allows, the procedures described above will be repeated for the breast and hematologic patients separately.

9.0 STUDY MANAGEMENT

9.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

9.2 Required Documentation

Before the study can be initiated at any site, the following documentation must be provided to the Clinical Protocol Office (CPO) at the University of North Carolina.

- A copy of the official IRB approval letter for the protocol and informed consent

- IRB membership list
- CVs and medical licensure for the principal investigator and any sub-investigators who will be involved in the study.
- Form FDA 1572 appropriately filled out and signed with appropriate documentation (NOTE: this is required if UNC holds the IND. Otherwise, the Investigator's signature documenting understanding of the protocol and providing commitment that this trial will be conducted according to all stipulations of the protocol is sufficient to ensure compliance)
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Executed clinical research contract

9.3 Registration Procedures

All patients must be registered with the CPO at the University of North Carolina before enrollment to study. To register a patient, call the Oncology Protocol Office at 919-966-4432 Monday through Friday, 9:00AM-5:00PM..

9.4 Data Management and Monitoring/Auditing

The CPO of the UNC LCCC will serve as the coordinating center for this trial. Data will be collected through a web based clinical research platform, OnCore®.

All data will be collected and entered into OnCore® by Clinical Research Associates (CRAs) from UNC LCCC. The investigators will allow monitors to review all source documents supporting data entered into OnCore®.

As an investigator initiated study, this trial will also be audited by the Lineberger Cancer Center audit committee every twelve months

9.5 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

9.5.1 Emergency Modifications

UNC investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior UNC or their respective institution's IRB/IEC approval/favorable opinion.

<u>For Institutions Relying on UNC's IRB:</u>
For any such emergency modification implemented, a UNC IRB modification form must be completed by UNC Research Personnel within five (5) business days of making the change.

9.5.2 Single Patient/Subject Exceptions

<u>For Institutions Relying on UNC's IRB:</u>

Any request to enroll a single subject who does not meet all the eligibility criteria of this study requires the approval of the UNC Principal Investigator and the UNC IRB.

9.5.3 Other Protocol Deviations/Violations

According to UNC's IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance meets any of the following criteria:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs please follow the guidelines below:

For Institutions Relying on UNC's IRB:
Protocol Deviations: UNC or Affiliate personnel will record the deviation in OnCore®, and report to any sponsor or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

Protocol Violations: Violations should be reported by UNC personnel within one (1) week of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems.

Unanticipated Problems:
UNC
Any events that meet the criteria for "Unanticipated Problems" as defined by UNC's IRB must be reported by the Study Coordinator using the IRB's web-based reporting system.

9.6 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator at UNC. It should also be noted that when an amendment to the protocol substantially alters the study

design or the potential risk to the patient, a revised consent form might be required.

For Institutions Relying on UNC's IRB:
The written amendment, and if required the amended consent form, must be sent to UNC's IRB for approval prior to implementation.

9.7 Record Retention

Study documentation includes all eCRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

9.8 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered into the eCRFs. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all eCRFs will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

10.0 REFERENCES

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11.0 APPENDICES

11.1 Appendix 1: Numerical Scale for Pain[6]:

If "0" is "no pain" and "10" is the worst pain you can imagine, what was your worst pain today?

11.2 Appendix 2: Neuropathic Pain Scale (ID Pain)[7]:

The *ID Pain* is a 6-item, patient-completed screening tool designed to help differentiate nociceptive and neuropathic pain. The items include:

1. Did the pain feel like pins and needles?
2. Did the pain feel hot/burning?
3. Did the pain feel numb?
4. Did the pain feel like electrical shocks?
5. Is the pain made worse with the touch of clothing or bed sheets?
6. Is the pain limited to your joints?

These questions will be asked of each patient by research staff via telephone twice during study medication administration after pegfilgrastim administration. A "yes" response to questions 1–5 are scored as 1. A "yes" response to question 6 is scored as−1.

Higher scores suggest a neuropathic component to the pain.

11.3 Appendix 3: Model Patient Pain Monitoring Log

Note: Patient will be instructed to begin log starting the day of pegfilgrastim administration. This form will also be used to record their pre-cycle 2 baseline score on the first pre-cycle 2 day of study medication dosing.

Date	**What is your worst pain score today on a scale of 0 to 10?** Remember that "0" is no pain and "10" is the worst pain you can imagine.	**What is your worst bone/joint pain score today on a scale of 0 to 10?** Remember that "0" is no bone/joint pain and "10" is the worst bone/joint pain you can imagine.	**Please list all pain medication and the doses of each on each day that you take your study medication.** Pain medication is any prescription or over-the-counter medicine you take for pain	**Why did you take the pain medication, to treat bone/joint pain or other type of pain? (check both if applicable)**
				Bone/joint pain _____ **Other pain** _____
				Bone/joint pain _____ **Other pain** _____
				Bone/joint pain _____ **Other pain** _____
				Bone/joint pain _____ **Other pain** _____
				Bone joint pain _____ **Other pain** _____
				Bone/joint pain _____ **Other pain** _____
				Bone/joint pain _____ **Other pain** _____
Pre-cycle 2				**Bone/joint pain** _____ **Other pain** _____

11.4 Appendix 4: Model Pregabalin/Placebo Medication Compliance Diary

Patient ID: ________ #tablets per dose: ___________ Signature and date: _________________________________

While you are on this study, please record the date and time you take your pregablin/placebo for each dose, and the number of tablets taken at each dose. Take your first daily dose of study medication at approximately the same time each day, and the second approximately 12 hours later. If a dose is vomited or if a dose is missed for any reason, the dose should not be made up. Please make a note on the diary when a dose was missed. Study medication may be taken with or without a meal; tablets should be swallowed whole with a glass of water, and should not be chewed or crushed. Please bring this diary to each appointment with your study doctor. You will be taking your study medication for 11 days in cycles 1 and 2, starting on the day you are instructed to begin. Please sign and date when completed.

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
Date: Time (AM): _______ Time (PM): _______	Date: Time (AM): _______ Time (PM): _______	Date: Time (AM): _______ Time (PM): _______	Date: Time (AM): _______ Time (PM): _______	Date: Time (AM): _______ Time (PM): _______	Date: Time (AM): _______ Time (PM): _______	Date: Time (AM): _______ Time (PM): _______
Date: Time (AM): _______ Time (PM): _______	Date: Time (AM): _______ Time (PM): _______	Date: Time (AM): _______ Time (PM): _______	Date: Time (AM): _______ Time (PM): _______	Date: Time (AM): _______ Time (PM): _______	Date: Time (AM): _______ Time (PM): _______	Date: Time (AM): _______ Time (PM): _______
Date: Time (AM): _______ Time (PM): _______	Date: Time (AM): _______ Time (PM): _______	Date: Time (AM): _______ Time (PM): _______	Date: Time (AM): _______ Time (PM): _______	Date: Time (AM): _______ Time (PM): _______	Date: Time (AM): _______ Time (PM): _______	Date: Time (AM): _______ Time (PM): _______