SUPPLEMENTAL MATERIAL

NOLAN: A randomized, phase 2 study to estimate the effect of prophylactic naproxen or loratadine vs no prophylactic treatment on bone pain in patients with early-stage breast cancer receiving chemotherapy and pegfilgrastim

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Full Listing of Inclusion and Exclusion Criteria

Inclusion Criteria

- Age ≥18 years
- Eastern Cooperative Oncology Group performance status ≤2
- Female with newly diagnosed, not previously treated with chemotherapy, stage I–III breast cancer
- Medically eligible to safely receive adjuvant or neoadjuvant chemotherapy, pegfilgrastim, naproxen, and loratadine as determined by the investigator
- Creatinine ≤ 1.5 x upper limit of normal
- Planning to receive at least 4 cycles of adjuvant or neoadjuvant chemotherapy
- Planning to receive prophylaxis with pegfilgrastim starting in the first cycle and continuing throughout each chemotherapy cycle of the treatment period
- Patient has provided informed consent

Exclusion Criteria

- History of other malignancy within the past 5 years, with the following exceptions:
  - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
  - Adequately treated cervical carcinoma in situ without evidence of disease
- Planning to receive weekly chemotherapy
- Ongoing chronic pain, or other painful conditions requiring treatment (including immediate post-operative treatment of surgical or procedural-associated pain) as determined by the investigator
- Chronic oral steroid use. Premedication related to the administration of chemotherapy, and use of antiemetics is allowed, per usual clinical practice

- Chronic use of oral nonsteroidal anti-inflammatory drugs or oral antihistamines outside of those dictated by the randomization groups outlined in the protocol, with the following exception:
  - Chronic oral aspirin use for cardiovascular-related indications
- Prior chemotherapy treatment for cancer within 5 years of current breast cancer diagnosis
- Prior use of granulocyte colony-stimulating factor
- History of clinically significant gastrointestinal (GI) bleeding, history of GI ulcers, or active GI bleeding within 6 months prior to randomization
- History of clinically significant bleeding disorders, thromboembolism within 6 months prior to randomization
- Currently enrolled in, or less than 30 days since ending, another clinical trial which includes language directing G-CSF (filgrastim, pegfilgrastim, other) or GM-CSF (sargramostim) use
- Currently enrolled in, or less than 30 days since ending, another interventional clinical trial that includes a blinded treatment or blinded treatment arm (whether or not the patient is randomized to the blinded arm)
  - Currently enrolled in, or less than 30 days since ending, another interventional clinical trial that includes the use of any agent not currently considered to be standard therapy for the adjuvant or neoadjuvant treatment of stage I–III breast cancer based on National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology for Breast Cancer
- Currently enrolled in, or less than 30 days since ending, any pain intervention study
- Female patients who are pregnant or lactating or of reproductive potential not willing to employ an effective method of birth control during treatment and for 17 days after discontinuing study treatment

- History or evidence of any other clinically significant disorder, condition, or disease (with the exception of those outlined above) that, in the opinion of the Investigator or Amgen, if consulted, would pose a risk to patient safety or interfere with the study evaluation, procedures or completion

Supplemental Table 1 Summary of chemotherapy regimens (full analysis set[a])

Chemotherapy regimen	No prophylaxis (N = 191) n (%)	Naproxen 500 mg BID (N = 196) n (%)	Loratadine 10 mg QD (N = 200) n (%)	Total (N = 587) n (%)
AC (doxorubicin, cyclophosphamide) Q3W	17 (8.9)	11 (5.6)	13 (6.5)	41 (7.0)
AC (doxorubicin, cyclophosphamide) Q4W	1 (0.5)	1 (0.5)	0 (0.0)	2 (0.3)
Dose-dense AC (doxorubicin, cyclophosphamide) Q2W	87 (45.5)	80 (40.8)	87 (43.5)	254 (43.3)
Dose-dense TC (docetaxel, cyclophosphamide) Q2W	3 (1.6)	0 (0.0)	1 (0.5)	4 (0.7)
EC (epirubicin, cyclophosphamide) Q2W	0 (0.0)	1 (0.5)	3 (1.5)	4 (0.7)
EC (epirubicin, cyclophosphamide) Q3W	3 (1.6)	3 (1.5)	3 (1.5)	9 (1.5)
FAC (5-fluorouracil, doxorubicin, cyclophosphamide) +/– sequential docetaxel +/– trastuzumab Q2W	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.2)
FAC (5-fluorouracil, doxorubicin, cyclophosphamide) +/– sequential docetaxel +/– trastuzumab Q3W	1 (0.5)	5 (2.6)	4 (2.0)	10 (1.7)
FEC (5-fluorouracil, epirubicin, cyclophosphamide) +/– sequential paclitaxel +/– trastuzumab Q3W	1 (0.5)	0 (0.0)	1 (0.5)	2 (0.3)
Other missing frequency	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.2)
Other Q2W	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.2)
Other Q3W	6 (3.1)	8 (4.1)	0 (0.0)	14 (2.4)
TAC (docetaxel, doxorubicin, cyclophosphamide) Q3W	18 (9.4)	10 (5.1)	8 (4.0)	36 (6.1)
TC (docetaxel, cyclophosphamide) Q3W	39 (20.4)	46 (23.5)	52 (26.0)	137 (23.3)
TCH (docetaxel, carboplatin, trastuzumab) +/– pertuzumab Q2W	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.2)
TCH (docetaxel, carboplatin, trastuzumab) +/– pertuzumab Q3W	25 (13.1)	35 (17.9)	35 (17.5)	95 (16.2)
TCH (docetaxel, carboplatin, trastuzumab) +/– pertuzumab Q4W	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)

N number of patients in the treatment group or total, *n* number of patients who received the specified regimen; *Q2W* once every 2 weeks; *Q3W* once every 3 weeks; *Q4W* once every 4 weeks. Percentages are calculated as n/N x 100

[a] The full analysis set includes all patients who received primary prophylaxis with pegfilgrastim

Supplemental Table 2 Patients with severe (grade 3 or 4) bone pain from AE reporting (full analysis set[a])

Grade 3 or 4 bone pain[b]	No prophylaxis (N = 191)	Naproxen 500 mg BID (N = 196)	Loratadine 10 mg QD (N = 200)	Difference (naproxen minus no prophylaxis)	Difference (loratadine minus no prophylaxis)	Difference (loratadine minus naproxen)
Cycle 1 – n (%)[c]	191 (100.0)	196 (100.0)	200 (100.0)			
Patients who reported bone pain	9	6	9			
Percentage	4.7	3.1	4.5	–1.7	–0.2	1.4
95% CI for percentage[d]	(2.2, 8.8)	(1.1, 6.5)	(2.1, 8.4)	(–6.0, 2.7)	(–4.9, 4.5)	(–2.8, 5.7)
Cycle 2 – n (%)[c]	178 (93.2)	180 (91.8)	193 (96.5)			
Patients who reported bone pain	2	3	0			
Percentage	1.1	1.7	0.0	0.5	–1.1	–1.7
95% CI for percentage[d]	(0.1, 4.0)	(0.3, 4.8)	(0.0, 1.9)	(–2.4, 3.5)	(–3.2, 1.0)	(–4.1, 0.7)
Cycle 3 – n (%)[c]	165 (86.4)	176 (89.8)	188 (94.0)			
Patients who reported bone pain	3	2	0			
Percentage	1.8	1.1	0.0	–0.7	–1.8	–1.1
95% CI for percentage[d]	(0.4, 5.2)	(0.1, 4.0)	(0.0, 1.9)	(–3.8, 2.5)	(–4.4, 0.8)	(–3.3, 1.0)
Cycle 4 – n (%)[c]	162 (84.8)	169 (86.2)	179 (89.5)			
Patients who reported bone pain	3	1	0			
Percentage	1.9	0.6	0.0	–1.3	–1.9	–0.6
95% CI for percentage[d]	(0.4, 5.3)	(0.0, 3.3)	(0.0, 2.0)	(–4.2, 1.7)	(–4.5, 0.8)	(–2.3, 1.1)
Across all cycles – n (%)[c]	191 (100.0)	196 (100.0)	200 (100.0)			
Patients who reported bone pain	11	8	9			

Percentage	5.8	4.1	4.5	–1.7	–1.3	0.4
95% CI for percentage[d]	(2.9, 10.1)	(1.8, 7.9)	(2.1, 8.4)	(–6.5, 3.2)	(–6.1, 3.6)	(–4.1, 4.9)

AE adverse event, *BID* twice a day, *CI* confidence interval, *N* number of patients in the analysis set, *QD* once a day

[a] The full analysis set includes all patients who received primary prophylaxis with pegfilgrastim

[b] This analysis was prespecified, but there were no reports of grade 4 bone pain.

[c] For individual cycles, n and percentage are based on the number of patients who entered the cycle. For across all cycles, n and percentage are based on the number of patients who started chemotherapy

[d] CIs for percentages are calculated using the binomial distribution. CIs for the difference between percentages are calculated using Fleiss's method with continuity correction

Supplemental Table 3 Patient-reported maximum bone pain (scale 0–10) by cycle and across all cycles: age <65 years (full analysis set[a])

Maximum patient-reported bone pain[b]	No prophylaxis (N = 156)	Naproxen 500 mg BID (N = 158)	Loratadine 10 mg QD (N = 162)	Difference (naproxen minus no prophylaxis)	Difference (loratadine minus no prophylaxis)	Difference (loratadine minus naproxen)
Cycle 1						
n[c]	156	158	162			
Mean (SE)	4.1 (0.3)	3.2 (0.3)	3.0 (0.2)	–0.9 (0.4)	–1.1 (0.3)	–0.2 (0.3)
95% CI[d]	(3.6, 4.6)	(2.7, 3.7)	(2.6, 3.5)	(–1.6, –0.2)	(–1.8, –0.4)	(–0.9, 0.5)
P value[d]				**0.015**	**0.002**	0.545
Cycle 2						
n[c]	147	148	158			
Mean (SE)	3.2 (0.3)	2.6 (0.2)	2.6 (0.2)	–0.6 (0.3)	–0.7 (0.3)	–0.0 (0.3)
95% CI[d]	(2.7, 3.7)	(2.1, 3.1)	(2.2, 3.0)	(–1.3, 0.0)	(–1.3, 0.0)	(–0.7, 0.6)
P value[d]				0.069	0.050	0.932
Cycle 3						
n[c]	136	144	153			
Mean (SE)	3.0 (0.3)	2.4 (0.2)	2.6 (0.2)	–0.5 (0.4)	–0.3 (0.3)	0.2 (0.3)
95% CI[d]	(2.4, 3.5)	(1.9, 2.9)	(2.2, 3.1)	(–1.2, 0.1)	(–1.0, 0.4)	(–0.4, 0.9)
P value[d]				0.118	0.369	0.465
Cycle 4						
n[c]	133	140	149			
Mean (SE)	3.0 (0.3)	2.3 (0.2)	2.3 (0.2)	–0.8 (0.4)	–0.8 (0.3)	–0.0 (0.3)
95% CI[d]	(2.5, 3.6)	(1.8, 2.8)	(1.8, 2.7)	(–1.5, –0.1)	(–1.4, –0.1)	(–0.7, 0.6)
P value[d]				**0.032**	**0.020**	0.946
Across all cycles						
n[c]	156	158	162			
Mean (SE)	5.0 (0.3)	4.3 (0.3)	4.2 (0.2)	–0.7 (0.4)	–0.9 (0.4)	–0.2 (0.4)
95% CI[d]	(4.5, 5.5)	(3.8, 4.8)	(3.7, 4.7)	(–1.4, 0.0)	(–1.6, –0.2)	(–0.9, 0.5)
P value[d]				0.057	**0.015**	0.626

Note: All missing values of patient-reported bone pain within any cycle were imputed. *P* values <0.05 are shown in bold

BID twice a day, *CI* confidence interval, *N* number of patients in the analysis set, *QD* once a day, *SE* standard error

[a] The full analysis set includes all patients who received primary prophylaxis with pegfilgrastim

[b] Maximum patient-reported bone pain is the maximum value of each patient's bone pain values across survey days 1–5 within each cycle. Across all cycles, the maximum is the maximum value of each patient's reported bone pain values across all survey days 1–5 across all cycles

[c] For individual cycles, n is based on the number of patients who entered the cycle. For across all cycles, n is based on the number of patients who started chemotherapy

[d] The 95% CI and *P* value are calculated using an analysis of variance (ANOVA) model, with differences calculated using pairwise least-squares mean differences

Supplemental Table 4 Patient-reported maximum bone pain (scale 0–10) by cycle and across all cycles: age ≥65 years (full analysis set[a])

Maximum patient-reported bone pain[b]	No prophylaxis (N = 35)	Naproxen 500 mg BID (N = 38)	Loratadine 10 mg QD (N = 38)	Difference (naproxen minus no prophylaxis)	Difference (loratadine minus no prophylaxis)	Difference (loratadine minus naproxen)
Cycle 1						
n[c]	35	38	38			
Mean (SE)	2.9 (0.5)	3.4 (0.5)	3.0 (0.5)	0.6 (0.8)	0.1 (0.7)	–0.4 (0.8)
95% CI[d]	(1.9, 3.9)	(2.4, 4.5)	(NA, NA)	(–0.9, 2.0)	(–1.3, 1.6)	(–1.9, 1.1)
P value[d]				0.463	0.846	0.586
Cycle 2						
n[c]	31	32	35			
Mean (SE)	1.8 (0.5)	1.6 (0.5)	2.4 (0.5)	–0.2 (0.7)	0.6 (0.7)	0.8 (0.7)
95% CI[d]	(0.9, 2.8)	(0.7, 2.5)	(1.4, 3.5)	(–1.5, 1.1)	(–0.8, 2.0)	(–0.5, 2.2)
P value[d]				0.711	0.421	0.238
Cycle 3						
n[c]	29	32	35			
Mean (SE)	1.7 (0.5)	1.3 (0.4)	2.0 (0.5)	–0.4 (0.6)	0.3 (0.7)	0.7 (0.6)
95% CI[d]	(0.8, 2.6)	(0.5, 2.1)	(1.1, 2.9)	(–1.6, 0.8)	(–1.0, 1.6)	(–0.5, 1.9)
P value[d]				0.534	0.677	0.286
Cycle 4						
n[c]	29	29	30			
Mean (SE)	1.7 (0.4)	1.3 (0.5)	1.6 (0.5)	–0.4 (0.6)	–0.1 (0.6)	0.3 (0.7)
95% CI[d]	(0.8, 2.5)	(0.4, 2.2)	(NA, NA)	(–1.7, 0.9)	(–1.3, 1.2)	(–1.0, 1.6)
P value[d]				0.547	0.925	0.613
Across all cycles						
n[c]	35	38	38			
Mean (SE)	3.3 (0.5)	3.8 (0.6)	3.5 (0.5)	0.5 (0.8)	0.2 (0.8)	–0.2 (0.8)
95% CI[d]	(2.2, 4.3)	(2.7, 4.9)	(2.5, 4.6)	(–1.0, 2.0)	(–1.3, 1.7)	(–1.8, 1.3)
P value[d]				0.531	0.755	0.753

Note: All missing values of patient-reported bone pain within any cycle were imputed

BID twice a day, *CI* confidence interval, *N* number of patients in the analysis set, *NA* not available, *QD* once a day, *SE* standard error

[a] The full analysis set includes all patients who received primary prophylaxis with pegfilgrastim

[b] Maximum patient-reported bone pain is the maximum value of each patient's bone pain values across survey days 1–5 within each cycle. Across all cycles, the maximum is the maximum value of each patient's reported bone pain values across all survey days 1–5 across all cycles

[c] For individual cycles, n is based on the number of patients who entered the cycle. For across all cycles, n is based on the number of patients who started chemotherapy

[d] The 95% CI and *P* value are calculated using an ANOVA model, with differences calculated using pairwise least-squares mean differences

Supplemental Table 5 Patient-reported maximum bone pain (scale 0–10) by cycle and across all cycles: taxane-based chemotherapy (full analysis set[a])

Maximum patient-reported bone pain[b]	No prophylaxis (N = 107)	Naproxen 500 mg BID (N = 111)	Loratadine 10 mg QD (N = 113)	Difference (naproxen minus no prophylaxis)	Difference (loratadine minus no prophylaxis)	Difference (loratadine minus naproxen)
Cycle 1						
n[c]	107	111	113			
Mean (SE)	4.7 (0.3)	4.0 (0.3)	3.8 (0.3)	–0.6 (0.4)	–0.9 (0.4)	–0.3 (0.4)
95% CI[d]	(4.0, 5.3)	(3.5, 4.6)	(3.2, 4.3)	(–1.5, 0.2)	(–1.7, –0.0)	(–1.1, 0.5)
P value[d]				0.161	**0.040**	0.498
Cycle 2						
n[c]	97	98	109			
Mean (SE)	3.4 (0.3)	2.8 (0.3)	3.3 (0.3)	–0.6 (0.4)	–0.1 (0.4)	0.5 (0.4)
95% CI[d]	(2.7, 4.0)	(2.2, 3.3)	(2.7, 3.8)	(–1.5, 0.3)	(–1.0, 0.8)	(–0.3, 1.3)
P value[d]				0.171	0.816	0.214
Cycle 3						
n[c]	86	97	105			
Mean (SE)	3.0 (0.3)	2.5 (0.3)	3.1 (0.3)	–0.5 (0.4)	0.1 (0.4)	0.6 (0.4)
95% CI[d]	(2.4, 3.7)	(2.0, 3.1)	(2.5, 3.6)	(–1.4, 0.4)	(–0.8, 0.9)	(–0.2, 1.4)
P value[d]				0.267	0.874	0.169
Cycle 4						
n[c]	84	91	97			
Mean (SE)	3.0 (0.3)	2.2 (0.3)	2.6 (0.3)	–0.8 (0.5)	–0.4 (0.4)	0.5 (0.4)
95% CI[d]	(2.4, 3.6)	(1.6, 2.8)	(2.1, 3.2)	(–1.7, 0.1)	(–1.2, 0.4)	(–0.4, 1.3)
P value[d]				0.070	0.375	0.277
Across all cycles						
n[c]	107	111	113			
Mean (SE)	5.3 (0.3)	4.7 (0.3)	4.9 (0.3)	–0.6 (0.4)	–0.4 (0.4)	0.2 (0.4)
95% CI[d]	(4.7, 5.9)	(4.1, 5.3)	(4.3, 5.4)	(–1.5, 0.2)	(–1.2, 0.4)	(–0.6, 1.0)
P value[d]				0.149	0.329	0.610

Note: All missing values of patient-reported bone pain within any cycle were imputed. *P* values <0.05 are shown in bold

BID twice a day, *CI* confidence interval, *N* number of patients in the analysis set, *QD* once a day, *SE* standard error

[a] The full analysis set includes all patients who received primary prophylaxis with pegfilgrastim

[b] Maximum patient-reported bone pain is the maximum value of each patient's bone pain values across survey days 1–5 within each cycle. Across all cycles, the maximum is the maximum value of each patient's reported bone pain values across all survey days 1–5 across all cycles

[c] For individual cycles, n is based on the number of patients who entered the cycle. For across all cycles, n is based on the number of patients who started chemotherapy

[d] The 95% CI and *P* value are calculated using an analysis of variance (ANOVA) model, with differences calculated using pairwise least-squares mean differences

Supplemental Table 6 Patient-reported maximum bone pain (scale 0–10) by cycle and across all cycles: non-taxane-based chemotherapy (full analysis set[a])

Maximum patient-reported bone pain[b]	No prophylaxis (N = 84)	Naproxen 500 mg BID (N = 85)	Loratadine 10 mg QD (N = 87)	Difference (naproxen minus no prophylaxis)	Difference (loratadine minus no prophylaxis)	Difference (loratadine minus naproxen)
Cycle 1						
n[c]	84	85	87			
Mean (SE)	2.9 (0.3)	2.3 (0.3)	2.1 (0.3)	–0.7 (0.5)	–0.9 (0.4)	–0.2 (0.4)
95% CI[d]	(2.3, 3.6)	(1.6, 2.9)	(1.5, 2.6)	(–1.6, 0.2)	(–1.7, –0.0)	(–1.0, 0.6)
P value[d]				0.148	**0.039**	0.642
Cycle 2						
n[c]	81	82	84			
Mean (SE)	2.6 (0.3)	2.0 (0.3)	1.6 (0.3)	–0.5 (0.4)	–0.9 (0.4)	–0.4 (0.4)
95% CI[d]	(2.0, 3.1)	(1.5, 2.6)	(1.1, 2.1)	(–1.3, 0.3)	(–1.7, –0.2)	(–1.2, 0.4)
P value[d]				0.222	**0.019**	0.301
Cycle 3						
n[c]	79	79	83			
Mean (SE)	2.4 (0.3)	1.8 (0.3)	1.8 (0.3)	–0.6 (0.4)	–0.6 (0.4)	–0.0 (0.4)
95% CI[d]	(1.8, 3.1)	(1.2, 2.4)	(1.3, 2.4)	(–1.5, 0.3)	(–1.5, 0.2)	(–0.8, 0.8)
P value[d]				0.165	0.147	0.981
Cycle 4						
n[c]	78	78	82			
Mean (SE)	2.6 (0.3)	2.0 (0.3)	1.6 (0.3)	–0.6 (0.5)	–1.0 (0.4)	–0.4 (0.4)
95% CI[d]	(1.9, 3.2)	(1.4, 2.6)	(1.0, 2.1)	(–1.4, 0.3)	(–1.9, –0.1)	(–1.2, 0.3)
P value[d]				0.219	**0.021**	0.268
Across all cycles						
n[c]	84	85	87			
Mean (SE)	4.0 (0.4)	3.7 (0.4)	3.0 (0.3)	–0.3 (0.5)	–1.0 (0.5)	–0.7 (0.5)
95% CI[d]	(3.3, 4.7)	(3.0, 4.4)	(2.4, 3.6)	(–1.3, 0.7)	(–1.9, –0.1)	(–1.6, 0.2)
P value[d]				0.535	**0.035**	0.144

Note: All missing values of patient-reported bone pain within any cycle were imputed. *P* values <0.05 are shown in bold

BID twice a day, *CI* confidence interval, *N* number of patients in the analysis set, *QD* once a day, *SE* standard error

[a] The full analysis set includes all patients who received primary prophylaxis with pegfilgrastim

[b] Maximum patient-reported bone pain is the maximum value of each patient's bone pain values across survey days 1–5 within each cycle. Across all cycles, the maximum is the maximum value of each patient's reported bone pain values across all survey days 1–5 across all cycles

[c] For individual cycles, n is based on the number of patients who entered the cycle. For across all cycles, n is based on the number of patients who started chemotherapy

[d] The 95% CI and *P* value are calculated using an analysis of variance (ANOVA) model, with differences calculated using pairwise least-squares mean differences

Supplemental Table 7 Patient-reported mean bone pain (scale 0–10) by cycle and across all cycles (full analysis set[a])

Mean patient-reported bone pain[b]	No prophylaxis (N = 191)	Naproxen 500 mg BID (N = 196)	Loratadine 10 mg QD (N = 200)	Difference (naproxen minus no prophylaxis)	Difference (loratadine minus no prophylaxis)	Difference (loratadine minus naproxen)
Cycle 1						
n[c]	191	196	200			
Mean (SE)	2.2 (0.2)	1.8 (0.2)	1.7 (0.1)	–0.3 (0.2)	–0.5 (0.2)	–0.2 (0.2)
95% CI[d]	(1.9, 2.5)	(1.5, 2.1)	(1.4, 1.9)	(–0.8, 0.1)	(–0.9, –0.1)	(–0.6, 0.2)
P value[d]				0.117	**0.016**	0.414
Cycle 2						
n[c]	178	180	193			
Mean (SE)	1.7 (0.2)	1.3 (0.1)	1.4 (0.1)	–0.4 (0.2)	–0.3 (0.2)	0.1 (0.2)
95% CI[d]	(1.4, 2.0)	(1.0, 1.6)	(1.1, 1.6)	(–0.8, 0.0)	(–0.7, 0.1)	(–0.3, 0.4)
P value[d]				0.080	0.135	0.741
Cycle 3						
n[c]	165	176	188			
Mean (SE)	1.6 (0.2)	1.3 (0.1)	1.4 (0.1)	–0.3 (0.2)	–0.2 (0.2)	0.1 (0.2)
95% CI[d]	(1.3, 1.9)	(1.0, 1.6)	(1.1, 1.7)	(–0.7, 0.1)	(–0.6, 0.2)	(–0.3, 0.5)
P value[d]				0.161	0.422	0.513
Cycle 4						
n[c]	162	169	179			
Mean (SE)	1.7 (0.2)	1.2 (0.1)	1.3 (0.1)	–0.5 (0.2)	–0.4 (0.2)	0.1 (0.2)
95% CI[d]	(1.4, 2.0)	(0.9, 1.5)	(1.1, 1.6)	(–0.9, –0.1)	(–0.8, 0.1)	(–0.3, 0.5)
P value[d]				**0.029**	0.098	0.536
Across all cycles						
n[c]	191	196	200			
Mean (SE)	1.9 (0.1)	1.5 (0.1)	1.5 (0.1)	–0.3 (0.2)	–0.4 (0.2)	–0.0 (0.2)
95% CI[d]	(1.6, 2.1)	(1.3, 1.8)	(1.3, 1.7)	(–0.7, 0.0)	(–0.7, –0.0)	(–0.4, 0.3)
P value[d]				0.088	**0.044**	0.801

Note: All missing values of patient-reported bone pain within any cycle were imputed. *P* values <0.05 are shown in bold
BID twice a day, *CI* confidence interval, *N* number of patients in the analysis set, *QD* once a day, *SE* standard error
[a] The full analysis set includes all patients who received primary prophylaxis with pegfilgrastim

[b] Mean of patient-reported bone pain values is the average of each patient's bone pain values across survey days 1–5 within each cycle. Across all cycles, the mean is the average of each patient-reported bone pain value across all survey days 1–5 across all cycles

[c] For individual cycles, n is based on the number of patients who entered the cycle. For across all cycles, n is based on the number of patients who started chemotherapy

[d] The 95% CI and *P* value are calculated using an analysis of variance (ANOVA) model, with differences calculated using pairwise least-squares mean differences

Supplemental Table 8 Patient-reported mean bone pain (scale 0–10) by cycle and across all cycles: age <65 years (full analysis set[a])

Mean patient-reported bone pain[b]	No prophylaxis (N = 156)	Naproxen 500 mg BID (N = 158)	Loratadine 10 mg QD (N = 162)	Difference (naproxen minus no prophylaxis)	Difference (loratadine minus no prophylaxis)	Difference (loratadine minus naproxen)
Cycle 1						
n[c]	156	158	162			
Mean (SE)	2.3 (0.2)	1.8 (0.2)	1.7 (0.2)	–0.5 (0.2)	–0.7 (0.2)	–0.1 (0.2)
95% CI[d]	(2.0, 2.7)	(1.5, 2.1)	(1.4, 2.0)	(–1.0, –0.1)	(–1.1, –0.2)	(–0.6, 0.3)
P value[d]				**0.028**	**0.006**	0.618
Cycle 2						
n[c]	147	148	158			
Mean (SE)	1.8 (0.2)	1.4 (0.2)	1.4 (0.1)	–0.4 (0.2)	–0.4 (0.2)	–0.0 (0.2)
95% CI[d]	(1.5, 2.2)	(1.1, 1.8)	(1.1, 1.7)	(–0.9, 0.1)	(–0.9, 0.0)	(–0.4, 0.4)
P value[d]				0.089	0.079	0.992
Cycle 3						
n[c]	136	144	153			
Mean (SE)	1.8 (0.2)	1.4 (0.2)	1.5 (0.2)	–0.4 (0.2)	–0.3 (0.2)	0.1 (0.2)
95% CI[d]	(1.4, 2.1)	(1.1, 1.7)	(1.2, 1.8)	(–0.9, 0.1)	(–0.8, 0.2)	(–0.3, 0.6)
P value[d]				0.108	0.254	0.602
Cycle 4						
n[c]	133	140	149			
Mean (SE)	1.8 (0.2)	1.3 (0.2)	1.4 (0.2)	–0.6 (0.2)	–0.4 (0.2)	0.1 (0.2)
95% CI[d]	(1.5, 2.2)	(1.0, 1.6)	(1.1, 1.7)	(–1.0, –0.1)	(–0.9, 0.0)	(–0.3, 0.6)
P value[d]				**0.020**	0.068	0.574
Across all cycles						
n[c]	156	158	162			
Mean (SE)	2.0 (0.2)	1.6 (0.1)	1.5 (0.1)	–0.5 (0.2)	–0.5 (0.2)	–0.0 (0.2)
95% CI[d]	(1.7, 2.4)	(1.3, 1.9)	(1.3, 1.8)	(–0.9, –0.0)	(–0.9, –0.1)	(–0.4, 0.4)
P value[d]				**0.029**	**0.016**	0.857

Note: All missing values of patient-reported bone pain within any cycle were imputed. *P* values <0.05 are shown in bold

BID twice a day, *CI* confidence interval, *N* number of patients in the analysis set, *QD* once a day, *SE* standard error

[a] The full analysis set includes all patients who received primary prophylaxis with pegfilgrastim

[b] Mean of patient-reported bone pain values is the average of each patient's bone pain values across survey days 1–5 within each cycle. Across all cycles, the mean is the average of each patient-reported bone pain value across all survey days 1–5 across all cycles

[c] For individual cycles, n is based on the number of patients who entered the cycle. For across all cycles, n is based on the number of patients who started chemotherapy

[d] The 95% CI and *P* value are calculated using an analysis of variance (ANOVA) model, with differences calculated using pairwise least-squares mean differences

Supplemental Table 9 Patient-reported mean bone pain (scale 0–10) by cycle and across all cycles: age ≥65 years (full analysis set[a])

Mean patient-reported bone pain[b]	No prophylaxis (N = 35)	Naproxen 500 mg BID (N = 38)	Loratadine 10 mg QD (N = 38)	Difference (naproxen minus no prophylaxis)	Difference (loratadine minus no prophylaxis)	Difference (loratadine minus naproxen)
Cycle 1						
n[c]	35	38	38			
Mean (SE)	1.5 (0.3)	2.0 (0.4)	1.6 (0.3)	0.5 (0.5)	0.1 (0.5)	–0.4 (0.5)
95% CI[d]	(0.8, 2.1)	(1.2, 2.7)	(NA, NA)	(–0.5, 1.5)	(–0.8, 1.0)	(–1.4, 0.6)
P value[d]				0.301	0.805	0.422
Cycle 2						
n[c]	31	32	35			
Mean (SE)	1.0 (0.3)	0.8 (0.3)	1.2 (0.3)	–0.2 (0.4)	0.2 (0.4)	0.4 (0.4)
95% CI[d]	(0.4, 1.6)	(0.3, 1.3)	(0.6, 1.7)	(–1.0, 0.6)	(–0.6, 1.0)	(–0.4, 1.2)
P value[d]				0.630	0.655	0.343
Cycle 3						
n[c]	29	32	35			
Mean (SE)	0.7 (0.2)	0.8 (0.3)	1.0 (0.3)	0.2 (0.4)	0.4 (0.4)	0.2 (0.4)
95% CI[d]	(0.2, 1.1)	(0.2, 1.4)	(0.5, 1.6)	(–0.6, 0.9)	(–0.4, 1.1)	(–0.6, 1.0)
P value[d]				0.694	0.321	0.617
Cycle 4						
n[c]	29	29	30			
Mean (SE)	1.0 (0.3)	0.9 (0.4)	1.0 (0.3)	–0.1 (0.5)	0.0 (0.4)	0.1 (0.5)
95% CI[d]	(0.4, 1.6)	(0.2, 1.6)	(NA, NA)	(–1.0, 0.8)	(–0.8, 0.9)	(–0.8, 1.0)
P value[d]				0.816	0.991	0.800
Across all cycles						
n[c]	35	38	38			
Mean (SE)	1.1 (0.2)	1.4 (0.3)	1.3 (0.3)	0.3 (0.4)	0.2 (0.4)	–0.1 (0.4)
95% CI[d]	(0.6, 1.5)	(0.8, 2.0)	(0.8, 1.8)	(–0.5, 1.1)	(–0.5, 0.9)	(–0.9, 0.7)
P value[d]				0.419	0.521	0.831

Note: All missing values of patient-reported bone pain within any cycle were imputed

BID twice a day, *CI* confidence interval, *N* number of patients in the analysis set, *NA* not available, *QD* once a day, *SE* standard error

[a] The full analysis set includes all patients who received primary prophylaxis with pegfilgrastim

[b] Mean of patient-reported bone pain values is the average of each patient's bone pain values across survey days 1–5 within each cycle. Across all cycles, the mean is the average of each patient-reported bone pain value across all survey days 1–5 across all cycles

[c] For individual cycles, n is based on the number of patients who entered the cycle. For across all cycles, n is based on the number of patients who started chemotherapy

[d] The 95% CI and *P* value are calculated using an analysis of variance (ANOVA) model, with differences calculated using pairwise least-squares mean differences

Supplemental Table 10 Patient-reported mean bone pain (scale 0–10) by cycle and across all cycles: taxane-based chemotherapy (full analysis set[a])

Mean patient-reported bone pain[b]	No prophylaxis (N = 107)	Naproxen 500 mg BID (N = 111)	Loratadine 10 mg QD (N = 113)	Difference (naproxen minus no prophylaxis)	Difference (loratadine minus no prophylaxis)	Difference (loratadine minus naproxen)
Cycle 1						
n[c]	107	111	113			
Mean (SE)	2.6 (0.2)	2.3 (0.2)	2.2 (0.2)	–0.3 (0.3)	–0.5 (0.3)	–0.2 (0.3)
95% CI[d]	(2.2, 3.1)	(1.9, 2.7)	(1.8, 2.6)	(–0.9, 0.3)	(–1.1, 0.1)	(–0.7, 0.4)
P value[d]				0.289	0.122	0.592
Cycle 2						
n[c]	97	98	109			
Mean (SE)	1.9 (0.2)	1.6 (0.2)	1.9 (0.2)	–0.3 (0.3)	–0.1 (0.3)	0.3 (0.3)
95% CI[d]	(1.5, 2.4)	(1.2, 2.0)	(1.5, 2.3)	(–1.0, 0.3)	(–0.7, 0.5)	(–0.3, 0.8)
P value[d]				0.286	0.838	0.335
Cycle 3						
n[c]	86	97	105			
Mean (SE)	1.8 (0.2)	1.5 (0.2)	1.8 (0.2)	–0.2 (0.3)	0.0 (0.3)	0.3 (0.3)
95% CI[d]	(1.3, 2.3)	(1.1, 2.0)	(1.4, 2.2)	(–0.9, 0.4)	(–0.6, 0.6)	(–0.3, 0.8)
P value[d]				0.450	0.957	0.382
Cycle 4						
n[c]	84	91	97			
Mean (SE)	1.8 (0.2)	1.4 (0.2)	1.7 (0.2)	–0.5 (0.3)	–0.1 (0.3)	0.3 (0.3)
95% CI[d]	(1.4, 2.3)	(0.9, 1.8)	(1.3, 2.1)	(–1.1, 0.2)	(–0.7, 0.5)	(–0.3, 0.9)
P value[d]				0.167	0.709	0.275
Across all cycles						
n[c]	107	111	113			
Mean (SE)	2.2 (0.2)	1.9 (0.2)	1.9 (0.2)	–0.3 (0.3)	–0.2 (0.3)	0.1 (0.3)
95% CI[d]	(1.8, 2.6)	(1.5, 2.2)	(1.6, 2.3)	(–0.8, 0.2)	(–0.7, 0.3)	(–0.4, 0.6)
P value[d]				0.296	0.399	0.811

Note: All missing values of patient-reported bone pain within any cycle were imputed

BID twice a day, *CI* confidence interval, *N* number of patients in the analysis set, *QD* once a day, *SE* standard error

[a] The full analysis set includes all patients who received primary prophylaxis with pegfilgrastim

[b] Mean of patient-reported bone pain values is the average of each patient's bone pain values across survey days 1–5 within each cycle. Across all cycles, the mean is the average of each patient-reported bone pain value across all survey days 1–5 across all cycles

[c] For individual cycles, n is based on the number of patients who entered the cycle. For across all cycles, n is based on the number of patients who started chemotherapy

[d] The 95% CI and *P* value are calculated using an analysis of variance (ANOVA) model, with differences calculated using pairwise least-squares mean differences

Supplemental Table 11 Patient-reported mean bone pain (scale 0–10) by cycle and across all cycles: non-taxane-based chemotherapy (full analysis set[a])

Mean patient-reported bone pain[b]	No prophylaxis (N = 84)	Naproxen 500 mg BID (N = 85)	Loratadine 10 mg QD (N = 87)	Difference (naproxen minus no prophylaxis)	Difference (loratadine minus no prophylaxis)	Difference (loratadine minus naproxen)
Cycle 1						
n[c]	84	85	87			
Mean (SE)	1.6 (0.2)	1.2 (0.2)	1.0 (0.2)	–0.4 (0.3)	–0.6 (0.3)	–0.2 (0.3)
95% CI[d]	(1.2, 2.0)	(0.8, 1.6)	(0.7, 1.3)	(–1.0, 0.2)	(–1.1, –0.1)	(–0.7, 0.3)
P value[d]				0.175	**0.024**	0.478
Cycle 2						
n[c]	81	82	84			
Mean (SE)	1.4 (0.2)	1.0 (0.2)	0.8 (0.1)	–0.4 (0.3)	–0.7 (0.2)	–0.2 (0.2)
95% CI[d]	(1.0, 1.8)	(0.7, 1.4)	(0.5, 1.0)	(–0.9, 0.1)	(–1.1, –0.2)	(–0.7, 0.2)
P value[d]				0.120	**0.007**	0.295
Cycle 3						
n[c]	79	79	83			
Mean (SE)	1.4 (0.2)	1.0 (0.2)	0.9 (0.2)	–0.4 (0.3)	–0.4 (0.3)	–0.0 (0.3)
95% CI[d]	(1.0, 1.8)	(0.6, 1.3)	(0.6, 1.2)	(–1.0, 0.1)	(–1.0, 0.1)	(–0.5, 0.5)
P value[d]				0.146	0.094	0.876
Cycle 4						
n[c]	78	78	82			
Mean (SE)	1.5 (0.2)	1.0 (0.2)	0.9 (0.2)	–0.5 (0.3)	–0.7 (0.3)	–0.1 (0.3)
95% CI[d]	(1.1, 2.0)	(0.7, 1.4)	(0.5, 1.2)	(–1.1, 0.0)	(–1.2, –0.1)	(–0.6, 0.4)
P value[d]				0.069	**0.023**	0.631
Across all cycles						
n[c]	84	85	87			
Mean (SE)	1.5 (0.2)	1.1 (0.2)	0.9 (0.1)	–0.4 (0.2)	–0.6 (0.2)	–0.2 (0.2)
95% CI[d]	(1.1, 1.8)	(0.8, 1.4)	(0.6, 1.2)	(–0.9, 0.1)	(–1.0, –0.1)	(–0.6, 0.3)
P value[d]				0.119	**0.014**	0.420

Note: All missing values of patient-reported bone pain within any cycle were imputed. *P* values <0.05 are shown in bold

BID twice a day, *CI* confidence interval, *N* number of patients in the analysis set, *QD* once a day, *SE* standard error

[a] The full analysis set includes all patients who received primary prophylaxis with pegfilgrastim

[b] Mean of patient-reported bone pain values is the average of each patient's bone pain values across survey days 1–5 within each cycle. Across all cycles, the mean is the average of each patient-reported bone pain value across all survey days 1–5 across all cycles

[c] For individual cycles, n is based on the number of patients who entered the cycle. For across all cycles, n is based on the number of patients who started chemotherapy

[d] The 95% CI and *P* value are calculated using an analysis of variance (ANOVA) model, with differences calculated using pairwise least-squares mean differences

Supplemental Table 12 Patient-reported AUC for bone pain by cycle and across all cycles (full analysis set[a])

Patient-reported bone pain AUC[b]	No prophylaxis (N=191)	Naproxen 500 mg BID (N=196)	Loratadine 10 mg QD (N=200)	Difference (naproxen minus no prophylaxis)	Difference (loratadine minus no prophylaxis)	Difference (loratadine minus naproxen)
Cycle 1						
n[c]	191	196	200			
Mean (SE)	9.3 (0.7)	7.7 (0.6)	7.0 (0.6)	–1.5 (0.9)	–2.3 (0.9)	–0.7 (0.9)
95% CI[d]	(7.9, 10.6)	(6.5, 9.0)	(5.8, 8.2)	(–3.4, 0.3)	(–4.0, –0.5)	(–2.5, 1.0)
P value[d]				0.100	**0.012**	0.393
Cycle 2						
n[c]	178	180	193			
Mean (SE)	7.3 (0.7)	5.6 (0.6)	5.9 (0.5)	–1.6 (0.9)	–1.4 (0.9)	0.2 (0.8)
95% CI[d]	(6.0, 8.5)	(4.4, 6.8)	(4.8, 6.9)	(–3.4, 0.1)	(–3.1, 0.3)	(–1.3, 1.8)
P value[d]				0.065	0.105	0.760
Cycle 3						
n[c]	165	176	188			
Mean (SE)	6.8 (0.7)	5.5 (0.6)	6.1 (0.6)	–1.3 (0.9)	–0.7 (0.9)	0.6 (0.8)
95% CI[d]	(5.5, 8.1)	(4.3, 6.7)	(4.9, 7.2)	(–3.1, 0.5)	(–2.5, 1.0)	(–1.1, 2.3)
P value[d]				0.143	0.404	0.491
Cycle 4						
n[c]	162	169	179			
Mean (SE)	7.2 (0.7)	5.2 (0.6)	5.6 (0.6)	–2.0 (0.9)	–1.6 (0.9)	0.5 (0.9)
95% CI[d]	(5.9, 8.6)	(3.9, 6.4)	(4.5, 6.8)	(–3.9, –0.2)	(–3.3, 0.2)	(–1.2, 2.1)
P value[d]				**0.027**	0.077	0.584
Across all cycles						
n[c]	191	196	200			
Mean (SE)	8.0 (0.6)	6.6 (0.5)	6.3 (0.5)	–1.4 (0.8)	–1.6 (0.8)	–0.2 (0.7)
95% CI[d]	(6.8, 9.1)	(5.5, 7.7)	(5.4, 7.3)	(–3.0, 0.2)	(–3.1, –0.1)	(–1.7, 1.2)
P value[d]				0.078	**0.033**	0.757

Note: All missing values of patient-reported bone pain within any cycle were imputed. *P* values <0.05 are shown in bold
AUC area under the curve, *BID* twice a day, *CI* confidence interval, *N* number of patients in the analysis set, *QD* once a day, *SE* standard error

[a] The full analysis set includes all patients who received primary prophylaxis with pegfilgrastim
[b] Patient-reported bone pain AUC is calculated using the trapezoidal rule with bone pain scores from day 1–5 for each cycle. The AUC across all cycles is the average of the AUCs across the cycles
[c] For individual cycles, n and percentage are based on the number of subjects who enter the cycle. For "All Cycles", n and percentage are based on the number of subjects who started chemotherapy
[d] The 95% CI and *P* value are calculated using an analysis of variance (ANOVA) model, with differences calculated using pairwise least-squares mean differences

Supplemental Table 13 Patient-reported AUC for bone pain by cycle and across all cycles: age <65 years (full analysis set[a])

Patient-reported bone pain AUC[b]	No prophylaxis (N=156)	Naproxen 500 mg BID (N=158)	Loratadine 10 mg QD (N=162)	Difference (naproxen minus no prophylaxis)	Difference (loratadine minus no prophylaxis)	Difference (loratadine minus naproxen)
Cycle 1						
n[c]	156	158	162			
Mean (SE)	9.9 (0.8)	7.6 (0.7)	7.1 (0.7)	–2.3 (1.0)	–2.9 (1.0)	–0.6 (1.0)
95% CI[d]	(8.4, 11.5)	(6.3, 9.0)	(5.8, 8.4)	(–4.3, –0.2)	(–4.8, –0.9)	(–2.5, 1.3)
P value[d]				**0.028**	**0.005**	0.555
Cycle 2						
n[c]	147	148	158			
Mean (SE)	7.9 (0.7)	6.1 (0.7)	6.0 (0.6)	–1.8 (1.0)	–1.8 (1.0)	–0.0 (0.9)
95% CI[d]	(6.4, 9.3)	(4.8, 7.4)	(4.8, 7.2)	(–3.8, 0.2)	(–3.7, 0.1)	(–1.8, 1.7)
P value[d]				0.075	0.060	0.960
Cycle 3						
n[c]	136	144	153			
Mean (SE)	7.6 (0.8)	5.9 (0.7)	6.4 (0.7)	–1.7 (1.0)	–1.2 (1.0)	0.5 (1.0)
95% CI[d]	(6.1, 9.2)	(4.6, 7.3)	(5.1, 7.7)	(–3.7, 0.3)	(–3.2, 0.8)	(–1.4, 2.4)
P value[d]				0.096	0.227	0.606
Cycle 4						
n[c]	133	140	149			
Mean (SE)	7.9 (0.8)	5.5 (0.7)	5.9 (0.6)	–2.4 (1.0)	–2.0 (1.0)	0.4 (0.9)
95% CI[d]	(6.4, 9.4)	(4.1, 6.8)	(4.6, 7.2)	(–4.4, –0.4)	(–3.9, –0.0)	(–1.4, 2.3)
P value[d]				**0.020**	**0.049**	0.654
Across all cycles						
n[c]	156	158	162			
Mean (SE)	8.7 (0.7)	6.7 (0.6)	6.5 (0.6)	–2.0 (0.9)	–2.2 (0.9)	–0.2 (0.8)
95% CI[d]	(7.4, 10.0)	(5.6, 7.9)	(5.4, 7.6)	(–3.7, –0.2)	(–3.9, –0.5)	(–1.9, 1.4)
P value[d]				**0.028**	**0.010**	0.770

Note: All missing values of patient-reported bone pain within any cycle were imputed. *P* values <0.05 are shown in bold
AUC area under the curve*, BID* twice a day, *CI* confidence interval, *N* number of patients in the analysis set, *QD* once a day, *SE* standard error

[a] The full analysis set includes all patients who received primary prophylaxis with pegfilgrastim
[b] Patient-reported bone pain AUC is calculated using the trapezoidal rule with bone pain scores from day 1–5 for each cycle. The AUC across all cycles is the average of the AUCs across the cycles
[c] For individual cycles, n and percentage are based on the number of subjects who enter the cycle. For "All Cycles", n and percentage are based on the number of subjects who started chemotherapy
[d] The 95% CI and *P* value are calculated using an analysis of variance (ANOVA) model, with differences calculated using pairwise least-squares mean differences

Supplemental Table 14 Patient-reported AUC for bone pain by cycle and across all cycles: age ≥65 years (full analysis set[a])

Patient-reported bone pain AUC[b]	No prophylaxis (N=35)	Naproxen 500 mg BID (N=38)	Loratadine 10 mg QD (N=38)	Difference (naproxen minus no prophylaxis)	Difference (loratadine minus no prophylaxis)	Difference (loratadine minus naproxen)
Cycle 1						
n[c]	35	38	38			
Mean (SE)	6.3 (1.3)	8.2 (1.6)	6.7 (1.4)	1.8 (2.1)	0.4 (2.0)	–1.5 (2.1)
95% CI[d]	(3.7, 9.0)	(5.1, 11.2)	(NA, NA)	(–2.2, 5.9)	(–3.5, 4.2)	(–5.6, 2.6)
P value[d]				0.374	0.854	0.481
Cycle 2						
n[c]	31	32	35			
Mean (SE)	4.3 (1.3)	3.4 (1.1)	5.0 (1.2)	–0.9 (1.7)	0.7 (1.7)	1.6 (1.7)
95% CI[d]	(1.8, 6.8)	(1.2, 5.6)	(2.7, 7.4)	(–4.2, 2.4)	(–2.7, 4.1)	(–1.7, 4.9)
P value[d]				0.590	0.686	0.333
Cycle 3						
n[c]	29	32	35			
Mean (SE)	2.8 (0.9)	3.4 (1.2)	4.5 (1.2)	0.6 (1.6)	1.6 (1.6)	1.0 (1.7)
95% CI[d]	(1.0, 4.7)	(1.0, 5.9)	(2.1, 6.8)	(–2.5, 3.7)	(–1.4, 4.7)	(–2.4, 4.4)
P value[d]				0.712	0.292	0.546
Cycle 4						
n[c]	29	29	30			
Mean (SE)	4.2 (1.3)	3.6 (1.4)	4.3 (1.3)	–0.5 (1.9)	0.1 (1.8)	0.6 (1.9)
95% CI[d]	(1.6, 6.7)	(0.8, 6.5)	(NA, NA)	(–4.4, 3.3)	(–3.4, 3.7)	(–3.1, 4.4)
P value[d]				0.783	0.952	0.736
Across all cycles						
n[c]	35	38	38			
Mean (SE)	4.7 (1.0)	5.9 (1.3)	5.7 (1.2)	1.2 (1.6)	1.0 (1.5)	–0.2 (1.7)
95% CI[d]	(2.7, 6.6)	(3.3, 8.4)	(3.4, 7.9)	(–2.0, 4.4)	(–2.1, 4.0)	(–3.6, 3.2)
P value[d]				0.472	0.530	0.908

Note: All missing values of patient-reported bone pain within any cycle were imputed

AUC area under the curve*, BID* twice a day, *CI* confidence interval, *N* number of patients in the analysis set, *NA* not available, *QD* once a day, *SE* standard error

[a] The full analysis set includes all patients who received primary prophylaxis with pegfilgrastim
[b] Patient-reported bone pain AUC is calculated using the trapezoidal rule with bone pain scores from day 1–5 for each cycle. The AUC across all cycles is the average of the AUCs across the cycles
[c] For individual cycles, n and percentage are based on the number of subjects who enter the cycle. For "All Cycles", n and percentage are based on the number of subjects who started chemotherapy
[d] The 95% CI and *P* value are calculated using an analysis of variance (ANOVA) model, with differences calculated using pairwise least-squares mean differences

Supplemental Table 15 Patient-reported AUC for bone pain by cycle and across all cycles: taxane-based chemotherapy (full analysis set[a])

Patient-reported bone pain AUC[b]	No prophylaxis (N=107)	Naproxen 500 mg BID (N=111)	Loratadine 10 mg QD (N=113)	Difference (naproxen minus no prophylaxis)	Difference (loratadine minus no prophylaxis)	Difference (loratadine minus naproxen)
Cycle 1						
n[c]	107	111	113			
Mean (SE)	11.3 (1.0)	10.0 (0.8)	9.3 (0.9)	–1.4 (1.3)	–2.1 (1.3)	–0.7 (1.2)
95% CI[d]	(9.4, 13.2)	(8.3, 11.6)	(7.5, 11.0)	(–3.9, 1.1)	(–4.6, 0.5)	(–3.1, 1.7)
P value[d]				0.285	0.109	0.557
Cycle 2						
n[c]	97	98	109			
Mean (SE)	8.2 (1.0)	6.8 (0.9)	7.9 (0.8)	–1.5 (1.3)	–0.3 (1.3)	1.2 (1.2)
95% CI[d]	(6.3, 10.2)	(5.1, 8.5)	(6.4, 9.5)	(–4.1, 1.1)	(–2.8, 2.2)	(–1.2, 3.5)
P value[d]				0.270	0.816	0.329
Cycle 3						
n[c]	86	97	105			
Mean (SE)	7.7 (1.0)	6.6 (0.9)	7.7 (0.9)	–1.1 (1.4)	0.0 (1.3)	1.1 (1.3)
95% CI[d]	(5.7, 9.7)	(4.8, 8.4)	(6.0, 9.4)	(–3.8, 1.6)	(–2.6, 2.6)	(–1.3, 3.6)
P value[d]				0.422	0.985	0.373
Cycle 4						
n[c]	84	91	97			
Mean (SE)	7.7 (1.0)	5.9 (1.0)	7.2 (0.8)	–1.8 (1.4)	–0.5 (1.3)	1.3 (1.3)
95% CI[d]	(5.8, 9.6)	(4.0, 7.8)	(5.6, 8.9)	(–4.5, 0.9)	(–3.0, 2.0)	(–1.2, 3.8)
P value[d]				0.181	0.698	0.300
Across all cycles						
n[c]	107	111	113			
Mean (SE)	9.2 (0.8)	8.0 (0.8)	8.2 (0.7)	–1.2 (1.1)	–1.0 (1.1)	0.2 (1.1)
95% CI[d]	(7.6, 10.9)	(6.5, 9.5)	(6.8, 9.6)	(–3.4, 1.0)	(–3.1, 1.2)	(–1.8, 2.3)
P value[d]				0.284	0.368	0.832

Note: All missing values of patient-reported bone pain within any cycle were imputed

AUC area under the curve*, BID* twice a day, *CI* confidence interval, *N* number of patients in the analysis set, *QD* once a day, *SE* standard error

[a] The full analysis set includes all patients who received primary prophylaxis with pegfilgrastim

[b] Patient-reported bone pain AUC is calculated using the trapezoidal rule with bone pain scores from day 1–5 for each cycle. The AUC across all cycles is the average of the AUCs across the cycles

[c] For individual cycles, n and percentage are based on the number of subjects who enter the cycle. For "All Cycles", n and percentage are based on the number of subjects who started chemotherapy

[d] The 95% CI and *P* value are calculated using an analysis of variance (ANOVA) model, with differences calculated using pairwise least-squares mean differences

Supplemental Table 16 Patient-reported AUC for bone pain by cycle and across all cycles: non-taxane-based chemotherapy (full analysis set[a])

Patient-reported bone pain AUC[b]	No prophylaxis (N=84)	Naproxen 500 mg BID (N=85)	Loratadine 10 mg QD (N=87)	Difference (naproxen minus no prophylaxis)	Difference (loratadine minus no prophylaxis)	Difference (loratadine minus naproxen)
Cycle 1						
n[c]	84	85	87			
Mean (SE)	6.7 (0.9)	4.8 (0.9)	4.1 (0.7)	–1.8 (1.2)	–2.6 (1.1)	–0.8 (1.1)
95% CI[d]	(5.0, 8.4)	(3.2, 6.5)	(2.8, 5.4)	(–4.2, 0.6)	(–4.7, –0.5)	(–2.9, 1.3)
P value[d]				0.135	**0.016**	0.475
Cycle 2						
n[c]	81	82	84			
Mean (SE)	6.1 (0.8)	4.2 (0.7)	3.1 (0.6)	–1.9 (1.1)	–2.9 (1.0)	–1.1 (0.9)
95% CI[d]	(4.4, 7.7)	(2.8, 5.7)	(2.0, 4.3)	(–4.0, 0.3)	(–4.9, –1.0)	(–2.9, 0.8)
P value[d]				0.094	**0.004**	0.257
Cycle 3						
n[c]	79	79	83			
Mean (SE)	5.8 (0.9)	4.1 (0.8)	4.0 (0.7)	–1.7 (1.2)	–1.9 (1.1)	–0.1 (1.0)
95% CI[d]	(4.1, 7.6)	(2.6, 5.6)	(2.6, 5.3)	(–4.0, 0.5)	(–4.1, 0.3)	(–2.2, 1.9)
P value[d]				0.134	0.093	0.900
Cycle 4						
n[c]	78	78	82			
Mean (SE)	6.7 (1.0)	4.3 (0.8)	3.8 (0.7)	–2.4 (1.2)	–2.9 (1.2)	–0.6 (1.0)
95% CI[d]	(4.7, 8.6)	(2.8, 5.8)	(2.3, 5.2)	(–4.8, 0.1)	(–5.3, –0.5)	(–2.6, 1.5)
P value[d]				0.057	**0.016**	0.594
Across all cycles						
n[c]	84	85	87			
Mean (SE)	6.4 (0.8)	4.7 (0.7)	3.9 (0.6)	–1.7 (1.0)	–2.5 (1.0)	–0.8 (0.9)
95% CI[d]	(4.9, 7.9)	(3.3, 6.1)	(2.7, 5.0)	(–3.7, 0.3)	(–4.4, –0.6)	(–2.6, 1.0)
P value[d]				0.103	**0.009**	0.380

Note: All missing values of patient-reported bone pain within any cycle were imputed. *P* values <0.05 are shown in bold

AUC area under the curve*, BID* twice a day, *CI* confidence interval, *N* number of patients in the analysis set, *QD* once a day, *SE* standard error

[a] The full analysis set includes all patients who received primary prophylaxis with pegfilgrastim

[b] Patient-reported bone pain AUC is calculated using the trapezoidal rule with bone pain scores from day 1–5 for each cycle. The AUC across all cycles is the average of the AUCs across the cycles

[c] For individual cycles, n and percentage are based on the number of subjects who enter the cycle. For "All Cycles", n and percentage are based on the number of subjects who started chemotherapy

[d] The 95% CI and *P* value are calculated using an analysis of variance (ANOVA) model, with differences calculated using pairwise least-squares mean differences

Supplemental Table 17 Patients with additional bone pain medications from medication logs (full analysis set[a])

	No prophylaxis (N=191)	Naproxen 500 mg BID (N=196)	Loratadine 10 mg QD (N=200)	Total (N=587)
Cycle 1				
n (%)[b]	191 (100.0)	196 (100.0)	200 (100.0)	587 (100.0)
Patients with bone pain medications	122	65	85	272
Percentage[c]	63.9	33.2	42.5	46.3
95% CI[d]	(56.6, 70.7)	(26.6, 40.2)	(35.6, 49.7)	(42.2, 50.5)
Cycle 2				
n (%)[b]	178 (93.2)	180 (91.8)	193 (96.5)	551 (93.9)
Patients with bone pain medications	88	47	75	210
Percentage[c]	49.4	26.1	38.9	38.1
95% CI[d]	(41.9, 57.0)	(19.9, 33.2)	(31.9, 46.1)	(34.0, 42.3)
Cycle 3				
n (%)[b]	165 (86.4)	176 (89.8)	188 (94.0)	529 (90.1)
Patients with bone pain medications	72	40	66	178
Percentage[c]	43.6	22.7	35.1	33.6
95% CI[d]	(35.9, 51.6)	(16.8, 29.6)	(28.3, 42.4)	(29.6, 37.9)
Cycle 4				
n (%)[b]	162 (84.8)	169 (86.2)	179 (89.5)	510 (86.9)
Patients with bone pain medications	72	42	60	174
Percentage[c]	44.4	24.9	33.5	34.1
95% CI[d]	(36.6, 52.4)	(18.5, 32.1)	(26.7, 40.9)	(30.0, 38.4)
All cycles				
n (%)[b]	191 (100.0)	196 (100.0)	200 (100.0)	587 (100.0)
Patients with bone pain medications	141	88	115	344
Percentage[c]	73.8	44.9	57.5	58.6
95% CI[d]	(67.0, 79.9)	(37.8, 52.1)	(50.3, 64.4)	(54.5, 62.6)

BID twice a day, *CI* confidence interval, *N* number of patients in the analysis set, *QD* once a day

[a] The full analysis set includes all patients who received primary prophylaxis with pegfilgrastim

[b] n = number of patients who entered the cycle. For all cycles, n = number of patients who started chemotherapy

[c] Percentage is based on the number of patients who entered the cycle. For all cycles, the percentage is based on the number of patients who started chemotherapy

[d] CI for the percentage is calculated using binomial distribution

Supplemental Table 18 Additional analgesics, antihistamines, and NSAIDs from medication logs by preferred term (full analysis set[a])

	No prophylaxis (N=191) n (%)	Naproxen 500 mg BID (N=196) n (%)	Loratadine 10 mg QD (N=200) n (%)	Total (N=587) n (%)
Number of patients with analgesics	126 (66.0)	84 (42.9)	99 (49.5)	309 (52.6)
Paracetamol	74 (38.7)	50 (25.5)	58 (29.0)	182 (31.0)
Ibuprofen	54 (28.3)	21 (10.7)	37 (18.5)	112 (19.1)
Vicodin	19 (9.9)	16 (8.2)	10 (5.0)	45 (7.7)
Oxycodone	9 (4.7)	5 (2.6)	7 (3.5)	21 (3.6)
Oxycocet	7 (3.7)	8 (4.1)	5 (2.5)	20 (3.4)
Hydrocodone	4 (2.1)	8 (4.1)	6 (3.0)	18 (3.1)
Tramadol	4 (2.1)	6 (3.1)	1 (0.5)	11 (1.9)
Thomapyrin N	3 (1.6)	0 (0.0)	1 (0.5)	4 (0.7)
Panadeine Co	1 (0.5)	2 (1.0)	0 (0.0)	3 (0.5)
Tramadol hydrochloride	2 (1.0)	1 (0.5)	0 (0.0)	3 (0.5)
Hydromorphone	2 (1.0)	0 (0.0)	0 (0.0)	2 (0.3)
Hydromorphone hydrochloride	1 (0.5)	0 (0.0)	1 (0.5)	2 (0.3)
Morphine	1 (0.5)	1 (0.5)	0 (0.0)	2 (0.3)
Oxycodone hydrochloride	0 (0.0)	0 (0.0)	2 (1.0)	2 (0.3)
Acetylsalicylic acid	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)
Acetylsalicylic acid with oxycodone	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.2)
Dozol	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)
Fentanyl	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.2)
Gabapentin	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.2)
Morphine sulfate	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.2)
Propacet	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.2)
Safapryn	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)
Number of patients with antihistamines	30 (15.7)	4 (2.0)	6 (3.0)	40 (6.8)
Loratadine	23 (12.0)	4 (2.0)	5 (2.5)	32 (5.5)
Cetirizine hydrochloride	6 (3.1)	0 (0.0)	0 (0.0)	6 (1.0)
Diphenhydramine	2 (1.0)	0 (0.0)	0 (0.0)	2 (0.3)
Fexofenadine hydrochloride	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)
Number of patients with NSAIDS	77 (40.3)	28 (14.3)	58 (29.0)	163 (27.8)
Ibuprofen	54 (28.3)	21 (10.7)	37 (18.5)	112 (19.1)
Naproxen sodium	27 (14.1)	3 (1.5)	20 (10.0)	50 (8.5)
Naproxen	5 (2.6)	8 (4.1)	5 (2.5)	18 (3.1)

Celecoxib	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.2)
Nabumetone	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.2)

Note: Analgesics does not include NSAIDs or antihistamines. Loratadine and naproxen listed here are in addition to doses given per protocol. WHODRUG version December 1, 2014 was used in the coding.

BID twice a day, *N* number of patients in the analysis set, *QD* once a day

[a] The full analysis set includes all patients who received primary prophylaxis with pegfilgrastim

Supplemental Table 19 Patient-reported bone pain in cycle 1 by survey day and range (full analysis set[a])

Patient-reported bone pain	No prophylaxis (N = 191)	Naproxen 500 mg BID (N = 196)	Loratadine 10 mg QD (N = 200)	Total (N = 587)
Survey day 1 score, n (%)[b,c]				
0	129 (67.5)	133 (67.9)	151 (75.5)	413 (70.4)
1–3	30 (15.7)	27 (13.8)	28 (14.0)	85 (14.5)
4–6	17 (8.9)	12 (6.1)	10 (5.0)	39 (6.6)
7–10	5 (2.6)	12 (6.1)	6 (3.0)	23 (3.9)
Missing	10 (5.2)	12 (6.1)	5 (2.5)	27 (4.6)
Survey day 2 score, n (%)[b,c]				
0	79 (41.4)	102 (52.0)	100 (50.0)	281 (47.9)
1–3	42 (22.0)	37 (18.9)	61 (30.5)	140 (23.9)
4–6	40 (20.9)	27 (13.8)	22 (11.0)	89 (15.2)
7–10	17 (8.9)	17 (8.7)	11 (5.5)	45 (7.7)
Missing	13 (6.8)	13 (6.6)	6 (3.0)	32 (5.5)
Survey day 3 score, n (%)[b,c]				
0	65 (34.0)	85 (43.4)	82 (41.0)	232 (39.5)
1–3	51 (26.7)	38 (19.4)	56 (28.0)	145 (24.7)
4–6	35 (18.3)	42 (21.4)	34 (17.0)	111 (18.9)
7–10	28 (14.7)	19 (9.7)	22 (11.0)	69 (11.8)
Missing	12 (6.3)	12 (6.1)	6 (3.0)	30 (5.1)
Survey day 4 score, n (%)[b,c]				
0	78 (40.8)	83 (42.3)	96 (48.0)	257 (43.8)
1–3	34 (17.8)	49 (25.0)	51 (25.5)	134 (22.8)
4–6	48 (25.1)	38 (19.4)	31 (15.5)	117 (19.9)
7–10	18 (9.4)	12 (6.1)	16 (8.0)	46 (7.8)
Missing	13 (6.8)	14 (7.1)	6 (3.0)	33 (5.6)
Survey day 5 score, n (%)[b,c]				
0	90 (47.1)	100 (51.0)	102 (51.0)	292 (49.7)
1–3	33 (17.3)	46 (23.5)	50 (25.0)	129 (22.0)
4–6	37 (19.4)	25 (12.8)	19 (9.5)	81 (13.8)
7–10	18 (9.4)	10 (5.1)	20 (10.0)	48 (8.2)
Missing	13 (6.8)	15 (7.7)	9 (4.5)	37 (6.3)

BID twice a day, *N* number of patients in the analysis set, *QD* once a day

[a] The full analysis set includes all patients who received primary prophylaxis with pegfilgrastim

[b] n = number of patients who entered cycle 1

[c] Percentage is based on the number of patients who entered cycle 1

Supplemental Table 20 Treatment emergent AEs in ≥5% of patients in any treatment arm by system organ class and preferred term (safety analysis set[a])

System Organ Class Preferred Term	No Prophylaxis (N = 196) n (%)	Naproxen 500 mg BID (N = 193) n (%)	Loratadine 10 mg QD (N = 198) n (%)
Number of patients reporting treatment emergent adverse events	188 (95.9)	192 (99.5)	194 (98.0)
Gastrointestinal disorders	159 (81.1)	171 (88.6)	157 (79.3)
Nausea	99 (50.5)	119 (61.7)	100 (50.5)
Constipation	60 (30.6)	78 (40.4)	66 (33.3)
Diarrhoea	68 (34.7)	75 (38.9)	71 (35.9)
Vomiting	34 (17.3)	45 (23.3)	29 (14.6)
Stomatitis	30 (15.3)	32 (16.6)	38 (19.2)
Dyspepsia	26 (13.3)	29 (15.0)	25 (12.6)
Gastrooesophageal reflux disease	16 (8.2)	16 (8.3)	12 (6.1)
Abdominal pain	14 (7.1)	11 (5.7)	5 (2.5)
General disorders and administration site conditions	148 (75.5)	148 (76.7)	157 (79.3)
Fatigue	120 (61.2)	110 (57.0)	128 (64.6)
Mucosal inflammation	18 (9.2)	21 (10.9)	23 (11.6)
Pyrexia	17 (8.7)	21 (10.9)	17 (8.6)
Oedema peripheral	18 (9.2)	17 (8.8)	19 (9.6)
Pain	25 (12.8)	17 (8.8)	22 (11.1)
Asthenia	10 (5.1)	8 (4.1)	9 (4.5)
Skin and subcutaneous tissue disorders	106 (54.1)	124 (64.2)	134 (67.7)
Alopecia	68 (34.7)	85 (44.0)	106 (53.5)
Rash	23 (11.7)	23 (11.9)	29 (14.6)
Pruritus	13 (6.6)	9 (4.7)	9 (4.5)
Dry skin	5 (2.6)	8 (4.1)	10 (5.1)
Musculoskeletal and connective tissue disorders	121 (61.7)	114 (59.1)	117 (59.1)
Bone pain	57 (29.1)	55 (28.5)	63 (31.8)
Arthralgia	28 (14.3)	31 (16.1)	24 (12.1)
Myalgia	23 (11.7)	18 (9.3)	22 (11.1)
Pain in extremity	19 (9.7)	17 (8.8)	22 (11.1)
Back pain	32 (16.3)	16 (8.3)	17 (8.6)

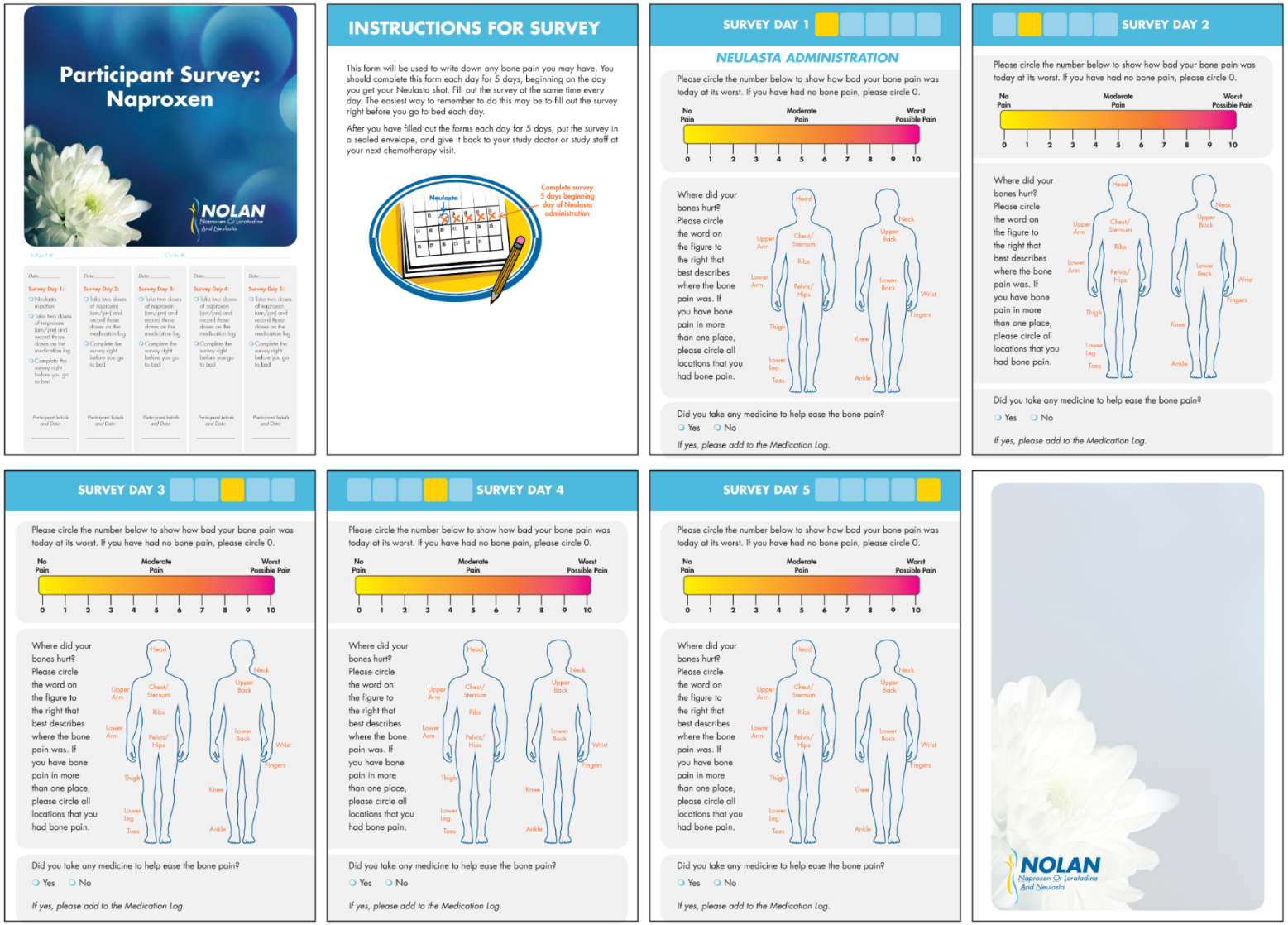
Nervous system disorders	103 (52.6)	108 (56.0)	112 (56.6)
Headache	49 (25.0)	54 (28.0)	48 (24.2)
Neuropathy peripheral	14 (7.1)	24 (12.4)	24 (12.1)
Dysgeusia	14 (7.1)	20 (10.4)	32 (16.2)
Dizziness	26 (13.3)	15 (7.8)	15 (7.6)
Peripheral sensory neuropathy	8 (4.1)	11 (5.7)	6 (3.0)
Blood and lymphatic system disorders	70 (35.7)	87 (45.1)	68 (34.3)
Anaemia	43 (21.9)	61 (31.6)	41 (20.7)
Neutropenia	21 (10.7)	27 (14.0)	27 (13.6)
Thrombocytopenia	7 (3.6)	15 (7.8)	9 (4.5)
Febrile neutropenia	11 (5.6)	14 (7.3)	4 (2.0)
Leukopenia	10 (5.1)	10 (5.2)	7 (3.5)
Lymphopenia	2 (1.0)	10 (5.2)	2 (1.0)
Infections and infestations	73 (37.2)	77 (39.9)	57 (28.8)
Urinary tract infection	9 (4.6)	13 (6.7)	3 (1.5)
Upper respiratory tract infection	12 (6.1)	8 (4.1)	6 (3.0)
Respiratory, thoracic and mediastinal disorders	72 (36.7)	71 (36.8)	76 (38.4)
Cough	22 (11.2)	25 (13.0)	23 (11.6)
Dyspnoea	22 (11.2)	18 (9.3)	16 (8.1)
Oropharyngeal pain	15 (7.7)	13 (6.7)	14 (7.1)
Epistaxis	9 (4.6)	9 (4.7)	17 (8.6)
Nasal congestion	2 (1.0)	6 (3.1)	13 (6.6)
Metabolism and nutrition disorders	68 (34.7)	68 (35.2)	66 (33.3)
Decreased appetite	36 (18.4)	34 (17.6)	39 (19.7)
Dehydration	24 (12.2)	17 (8.8)	14 (7.1)
Hypokalaemia	12 (6.1)	17 (8.8)	13 (6.6)
Hyperglycaemia	9 (4.6)	10 (5.2)	7 (3.5)
Psychiatric disorders	44 (22.4)	52 (26.9)	49 (24.7)
Insomnia	22 (11.2)	35 (18.1)	31 (15.7)
Anxiety	16 (8.2)	20 (10.4)	11 (5.6)
Depression	11 (5.6)	6 (3.1)	7 (3.5)
Investigations	35 (17.9)	37 (19.2)	38 (19.2)
White blood cell count decreased	13 (6.6)	7 (3.6)	10 (5.1)
Neutrophil count decreased	7 (3.6)	4 (2.1)	10 (5.1)

Vascular disorders	37 (18.9)	28 (14.5)	30 (15.2)
Hot flush	16 (8.2)	12 (6.2)	16 (8.1)

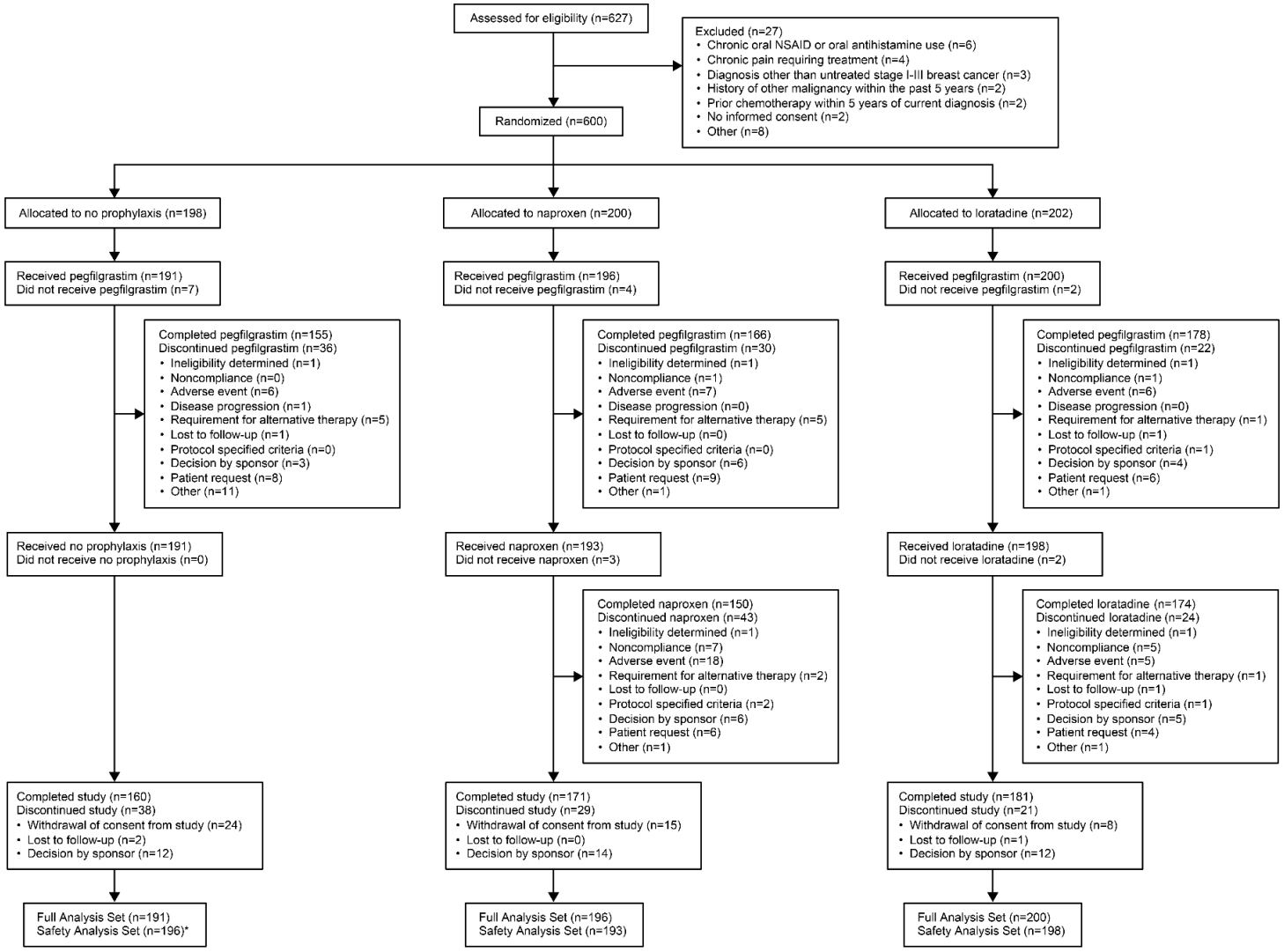
AE adverse event, *BID* twice a day, *QD* once a day

[a] The safety analysis set includes all patients who received primary prophylaxis with pegfilgrastim; allocation to treatment groups is based on prophylactic medication actually received

Supplemental Fig. 1 Naproxen bone pain survey

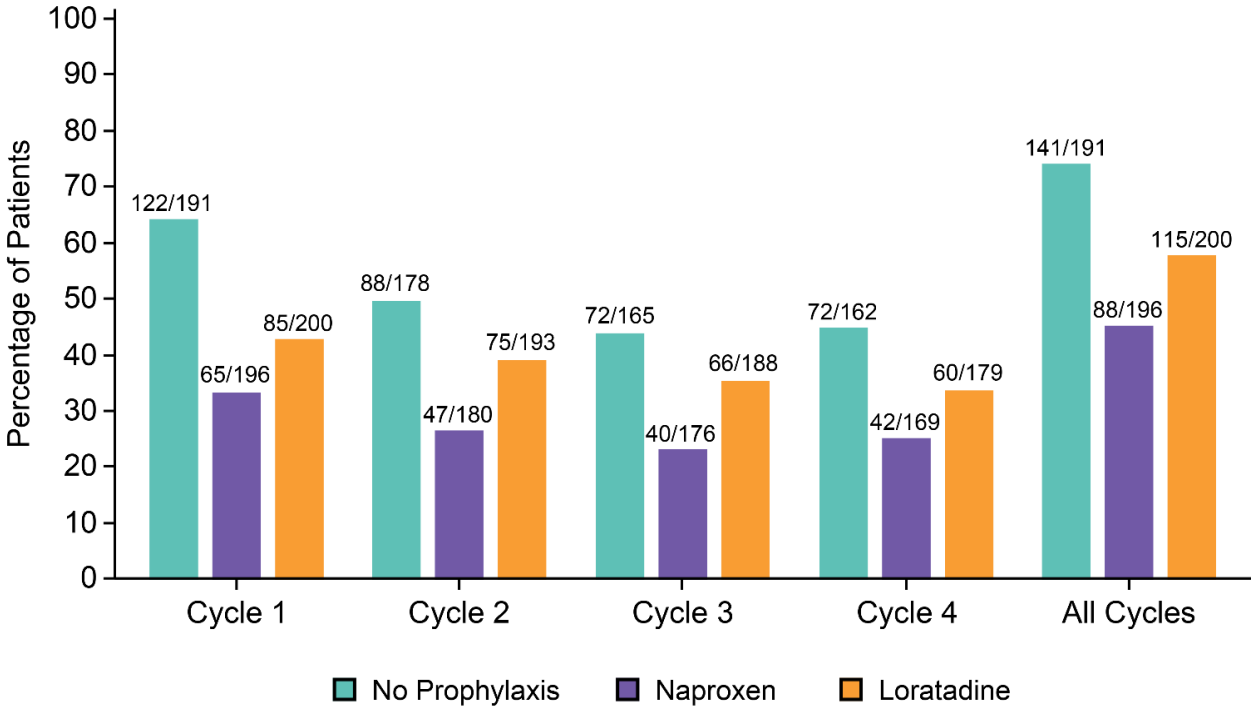


Supplemental Fig. 2 CONSORT Diagram



*2 patients in the naproxen group and 3 patients in the loratadine group never received prophylaxis; these 5 patients are included in the safety analysis set for the no prophylaxis group.

Supplemental Fig. 3 Percentage of patients with additional bone pain medications from medication logs (full analysis set)



Supplemental Fig. 4 Distribution of patient-reported bone pain in cycle 1 by cycle day (full analysis set). *L* loratadine, *N* naproxen, *NP* no prophylaxis