2018

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VIENNA, AUSTRIA

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Eflapegrastim is safe and effective in reducing severe neutropenia in patients treated with myelosuppressive chemotherapy in ADVANCE, a Phase 3 randomized controlled trial compared to pegfilgrastim

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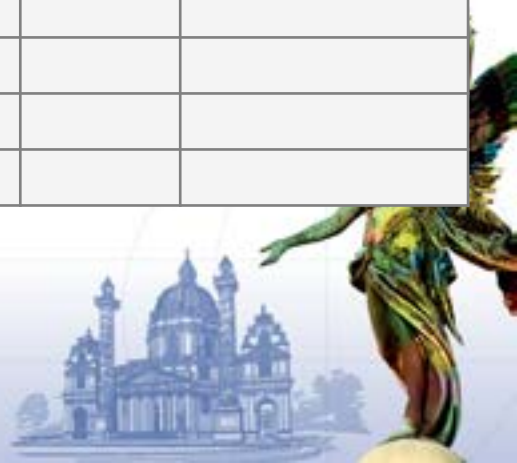
Abstract Number: MSCC8-0813

Faculty Disclosure

Company Name	*Honoraria/ Expenses*	*Consulting/ Advisory Board*	*Funded Research*	*Royalties/ Patent*	*Stock Options*	*Ownership/ Equity Position*	*Employee*	*Other (please specify)*
Spectrum Pharmaceuticals			x					



Eflapegrastim (SPI-2012) for the Management of Chemotherapy-Induced Neutropenia

A Novel, Long-Acting GCSF

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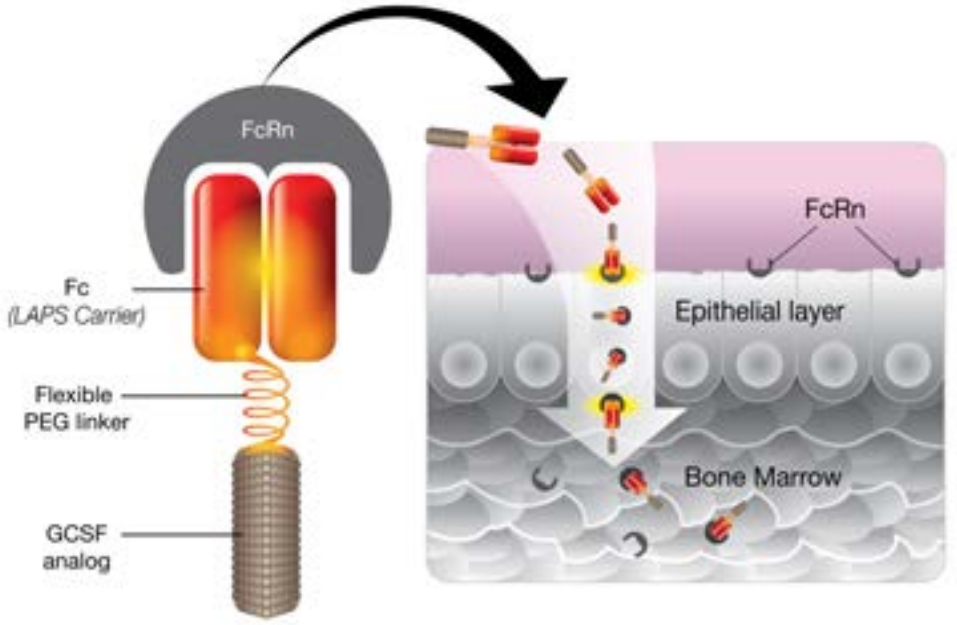
- Novel biologic chemically conjugated form of recombinant human G-CSF analogue
- Fc-mediated transport of G-CSF leads to increased bone marrow uptake
- Decreased renal and vascular endothelial clearance
- Higher distribution of eflapegrastim in bone marrow along with stronger stem cell proliferation could improve efficacy



Eflapegrastim Phase 2 Efficacy

Median Absolute Neutrophil Count (ANC) Over Time in Cycle 1

- Dose-ranging, active control study with three dose levels of eflapegrastim
- Patients candidates for neoadjuvant chemotherapy with TC
- TC dosing on Day 1, G-CSF dosing on Day 2 of each of 4 cycles
- Significant dose response to the reduction in severe neutropenia
- 135 µg/kg of eflapegrastim non-inferior, 270 µg/kg eflapegrastim statistically superior to pegfilgrastim in the reduction of severe neutropenia
- Safety profile of eflapegrastim similar to pegfilgrastim

	Eflapegrastim 45 µg/kg (N=39)	Eflapegrastim 135 µg/kg (N=36)	Eflapegrastim 270 µg/kg (N=36)	Pegfilgrastim 6 mg (N=36)
Days of Severe Neutropenia or DSN (Days) in Cycle 1				
Mean (SD)	1.03 (1.547)	0.44 (1.275)	0.03 (0.167)	0.31 (0.822)
Difference with Pegfilgrastim	0.72	0.14	-0.28	N/A
Non-inferiority *p*-value	0.296	0.002	<0.001	N/A
Superiority *p*-value	0.006	0.528	0.023	N/A

ADVANCE Study Overview

- R**and**omized Trial of **SPI-2012 V**ersus Pegfilgrastim in the Management of Chemotherapy Induced Neutropenia in Breast C**ance**r Patients Receiving Docetaxel and Cyclophosphamide (TC) (**ADVANCE**)
- **Primary Endpoint and Test:** Non-inferiority of eflapegrastim to pegfilgrastim in duration of severe neutropenia (DSN) in Cycle 1
- **Key Secondary Endpoints:**
  - Time to absolute neutrophil count (ANC) recovery in Cycle 1
  - Depth of ANC Nadir, defined as the patient's lowest ANC in Cycle 1
  - Incidence of Febrile Neutropenia (FN) in patients during Cycle 1
  - Safety
- **Study Drug:**
  - SPI-2012 (eflapegrastim, Rolontis) – fixed dose, 3.6 mg GCSF equivalent
  - Pegfilgrastim – fixed dose, 6 mg GCSF equivalent
- **Number of Patients:** 406 (1:1 randomization)
- **Target Population:** Patients with new diagnosis of early-stage breast cancer who are candidates for adjuvant or neo-adjuvant treatment with TC chemotherapy

Demographics and Baseline Characteristics

Category		Eflapegrastim (N=196) n (%)	Pegfilgrastim (N=210) n (%)	Total (N=406) n (%)
Age	Mean (SD) Median (min, max)	59.9 (11.12) 61.0 (28, 83)	59.0 (11.79) 60 (24, 84)	59.5 (11.47) 61.0 (24, 84)
	<65 yrs	118 (60)	129 (61)	247 (61)
	≥ 65 yrs	78 (40)	81 (39)	159 (39)
Race	White or Caucasian	156 (80)	159 (76)	315 (78)
	Black or African American	26 (13)	32 (15)	58 (14)
	Others	14 (7)	19 (9)	33 (8)
Weight (kg)	Mean (SD) Median (min, max)	80.3 (17.38) 78.6 (42, 145)	81.5 (20.11) 78.7 (42, 150)	80.9 (18.83) 78.6 (42, 150)
	≤75 kg	81 (41)	93 (44)	174 (43)
	>75 kg	115 (59)	117 (56)	232 (57)
ECOG	0	140 (71)	147 (70)	287 (71)
	1	56 (29)	59 (28)	115 (28)
	2	0	4 (2)	4 (1)

Chemotherapy and Study Drug Exposure

- Patients were well compliant with the chemotherapy across all cycles
  - Docetaxel: >99% in both treatment arms in Cycle 1,
  - Cyclophosphamide: >99% in both treatment arms in Cycle 1
  - ≤2% out of compliance to docetaxel and cyclophosphamide across all cycles
- 100% compliance eflapegrastim and pegfilgrastim in Cycle 1

Summary of Patient Disposition

	Eflapegrastim N (%)	Pegfilgrastim N (%)	Total N (%)
Intent-to-Treat Population	196	210	406
Safety Population	197	208	405*
Completed Treatment Cycles			
Cycle 1	194 (99)	208 (99)	402 (99)
Cycle 2	181 (92)	190 (90)	371 (91)
Cycle 3	176 (90)	182 (87)	358 (88)
Cycle 4	168 (86)	179 (85)	347 (85)
Discontinued from Treatment	28 (14)	30 (14)	58 (14)
Adverse Event	9 (5)	10 (5)	19 (5)
Discontinuation of Eflapegrastim or Pegfilgrastim	3 (2)	0	3 (1)
Delay of TC for > 42 days since last study treatment	0	1 (<1)	1 (<1)
Investigator Decision	2 (1)	6 (3)	8 (2)
Sponsor Decision	0	1 (<1)	1 (<1)
Withdrawal of Informed Consent	12 (6)	11 (5)	23 (6)
Death	0	1 (<1)	1 (<1)
Other	2 (1)	0	2 (<1)

*1 patient randomized to pegfilgrastim but received eflapegrastim; 1 patient randomized to pegfilgrastim but never received the drug

Primary Efficacy Endpoint– DSN in Cycle 1 (ITT Population)

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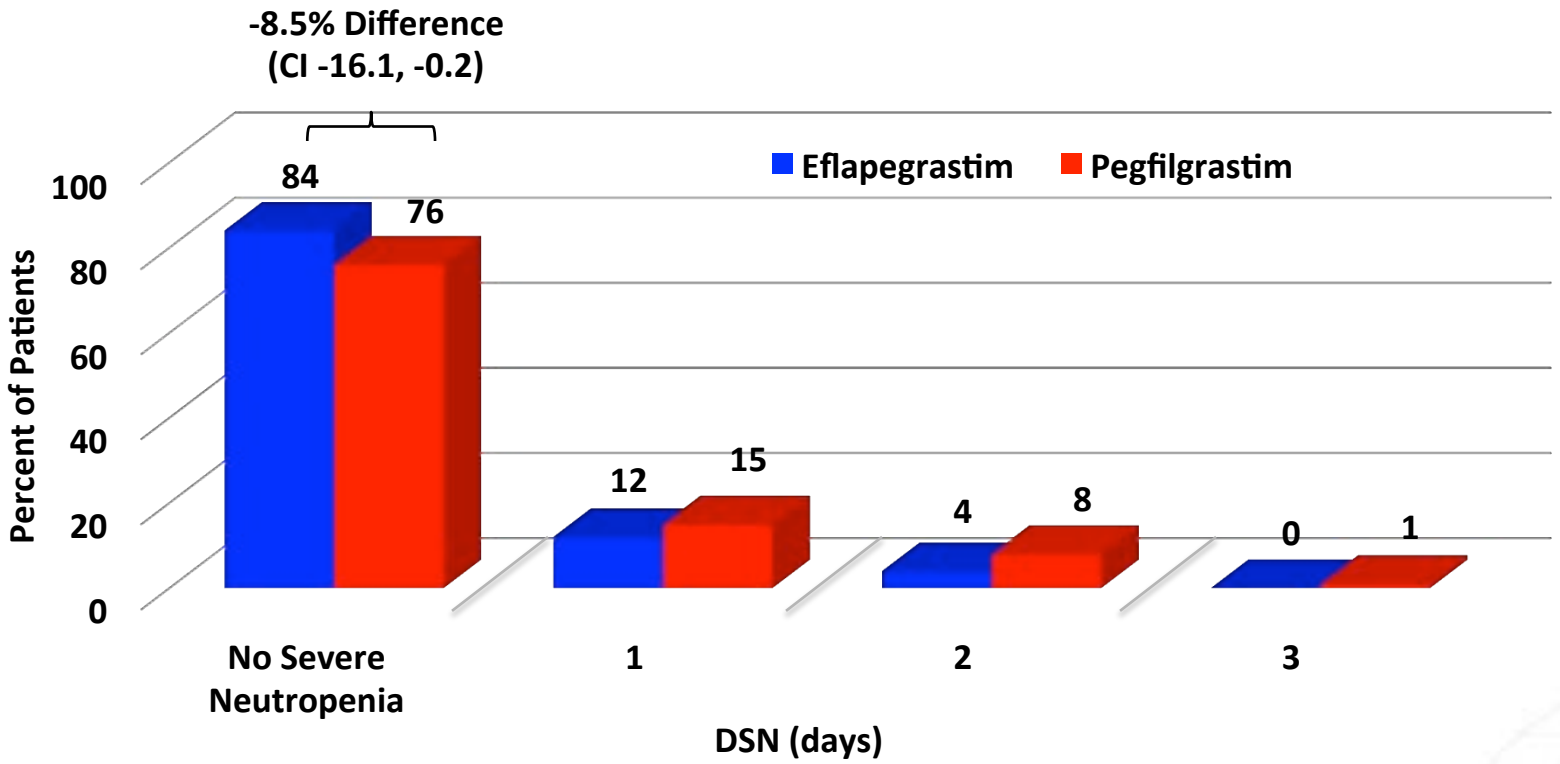
	Eflapegrastim N=196	Pegfilgrastim N=210
DSN (days) Mean (SD) Median (Range)	0.19 (0.478) 0 (0, 2)	0.34 (0.668) 0 (0, 3)
Difference in mean DSN (Eflapegrastim – pegfilgrastim) Percentile Method: Confidence Interval* Non-inferiority p-value**	**-0.148** (-0.260, -0.035) <0.0001	

Non-inferiority met as the upper bound of 95% CI is <0.62 day.

*95% CI was calculated using bootstrap resampling of the data; ** p-value is based on the calculated t-statistic from bootstrapped sample mean and standard error

Frequency of Severe Neutropenia in Cycle 1 (ITT Population)

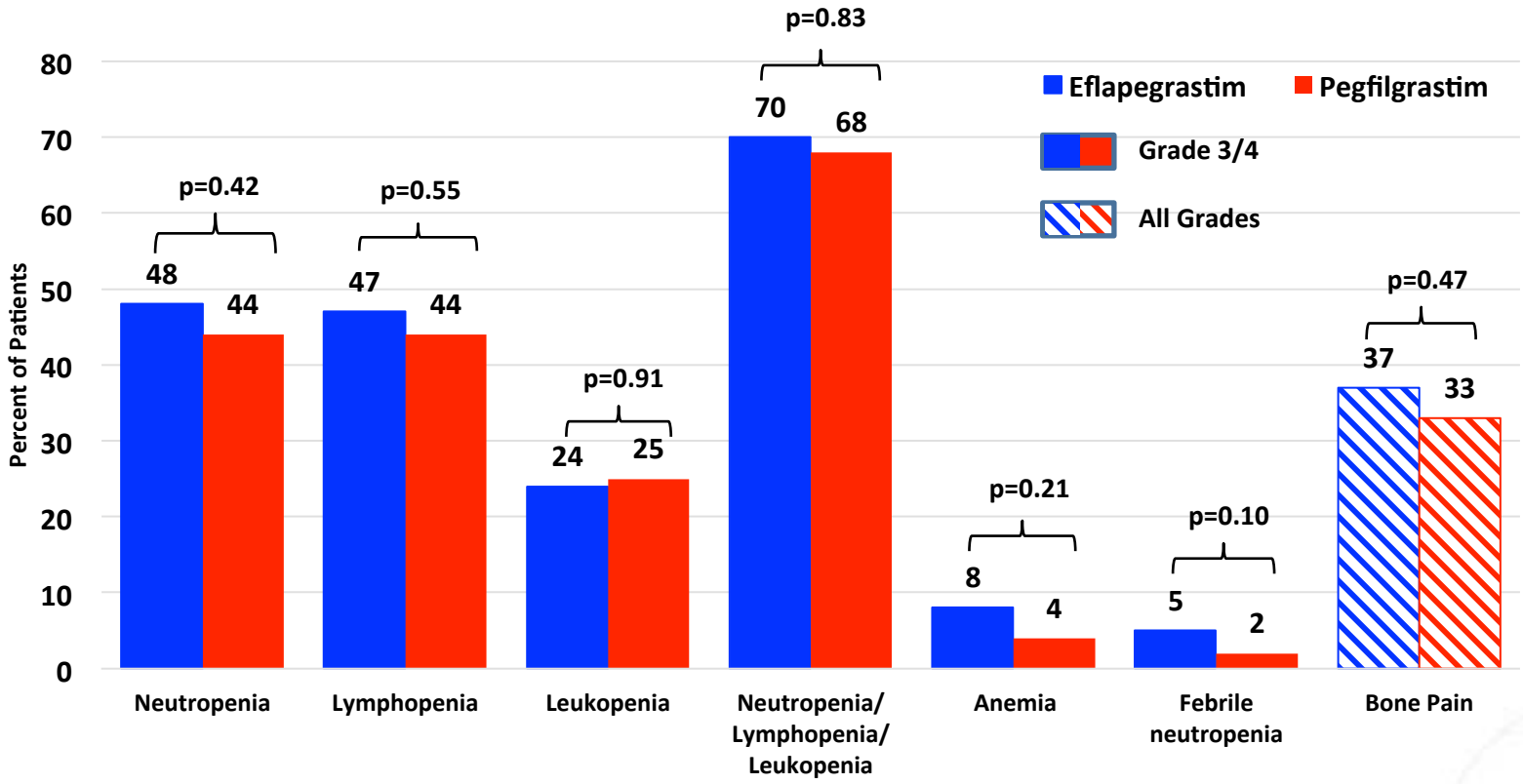


*95% CI was calculated using Clopper-Pearson method

Summary of DSN in Cycle 2 to 4
(ITT Population)

	Eflapegrastim N=196	Pegfilgrastim N=210
Cycle 2 Mean (SD) Median (Range)	0.13 (0.349) 0 (0, 2)	0.08 (0.266) 0 (0, 1)
Difference in mean DSN (eflapegrastim – pegfilgrastim) Percentile Method: Confidence Interval* Non-Inferiority p-value**	0.051 (-0.008, 0.112) <0.0001	
Cycle 3 Mean (SD) Median (Range)	0.11 (0.326) 0 (0, 2)	0.08 (0.273) 0 (0, 1)
Difference in mean DSN (eflapegrastim – pegfilgrastim) Percentile Method: Confidence Interval* Non-Inferiority p-value**	0.026 (-0.032, 0.085) <0.0001	
Cycle 4 Mean (SD) Median (Range)	0.10 (0.303) 0 (0, 1)	0.09 (0.281) 0 (0, 1)
Difference in mean DSN (eflapegrastim – pegfilgrastim) Percentile Method: Confidence Interval* Non-inferiority p-value**	0.016 (-0.039, 0.072) <0.0001	

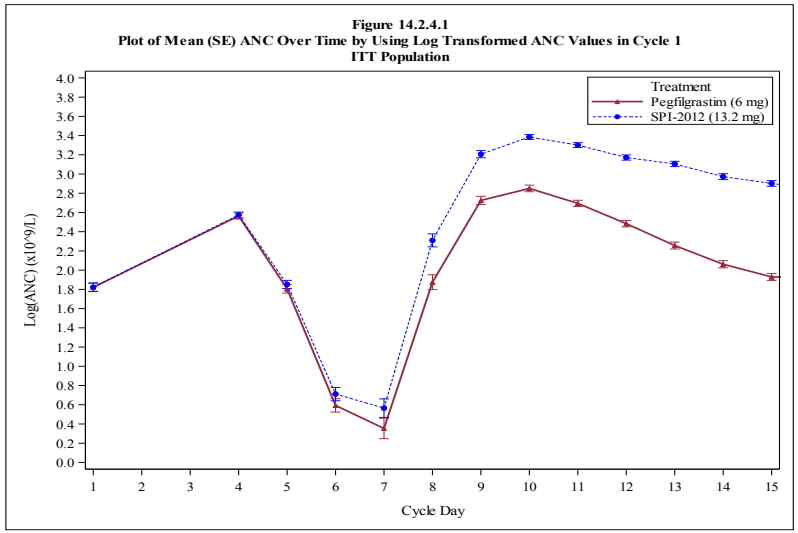
Summary of Most Common Grade 3-4 Adverse Events (AE >5%)

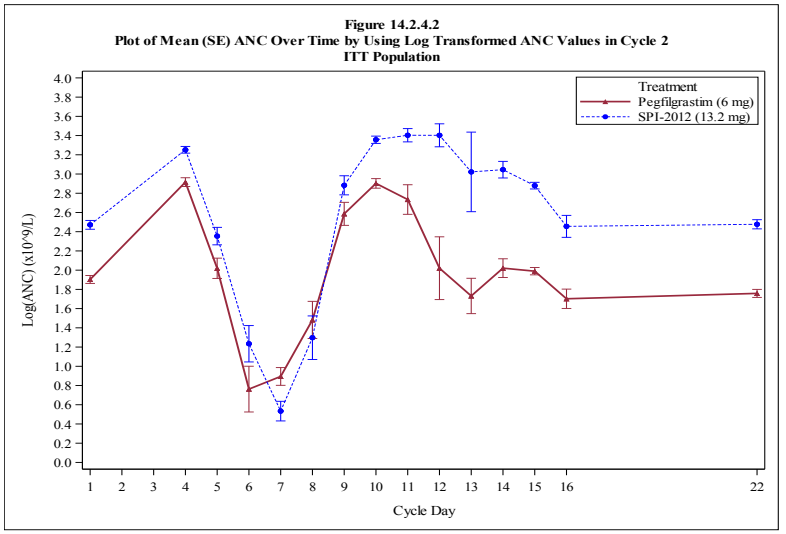


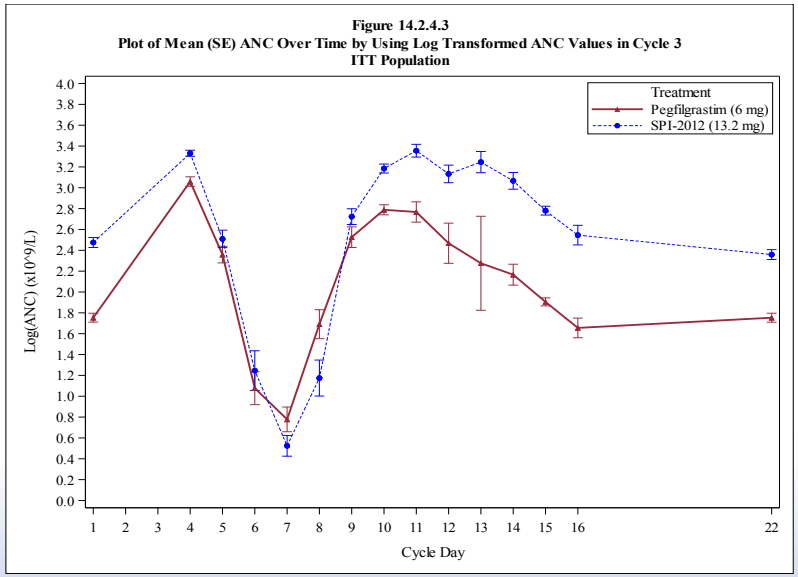
Summary and Conclusions

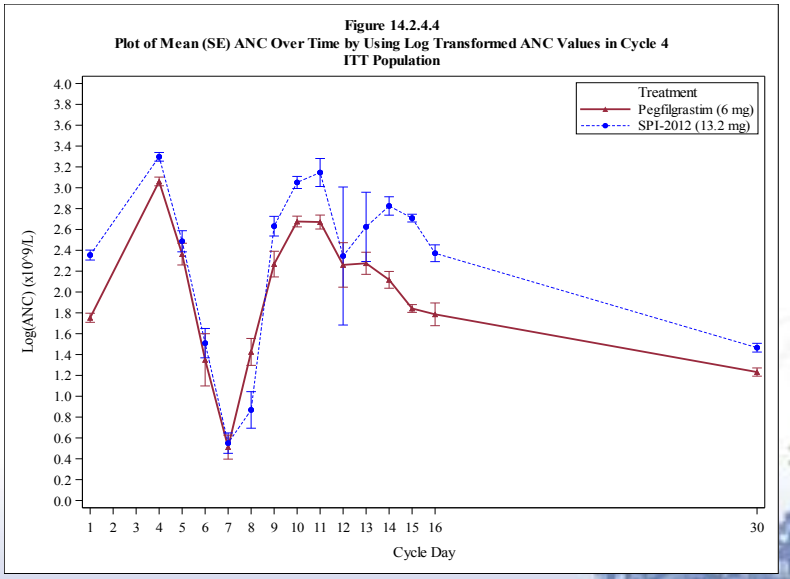
- Primary efficacy endpoint of non-inferiority of eflapegrastim to pegfilgrastim in mean DSN in Cycle 1 was met
- Mean DSNs were similar between eflapegrastim and pegfilgrastim and the study demonstrated non-inferiority in Cycles 2 to 4.
- Most common adverse events were hematologic with similar rates of Grade 3-4 events between treatment groups
- Grade 3-4 bone pain rates were similar between treatment groups and were ≤5% in each group.

ANC profile across cycles





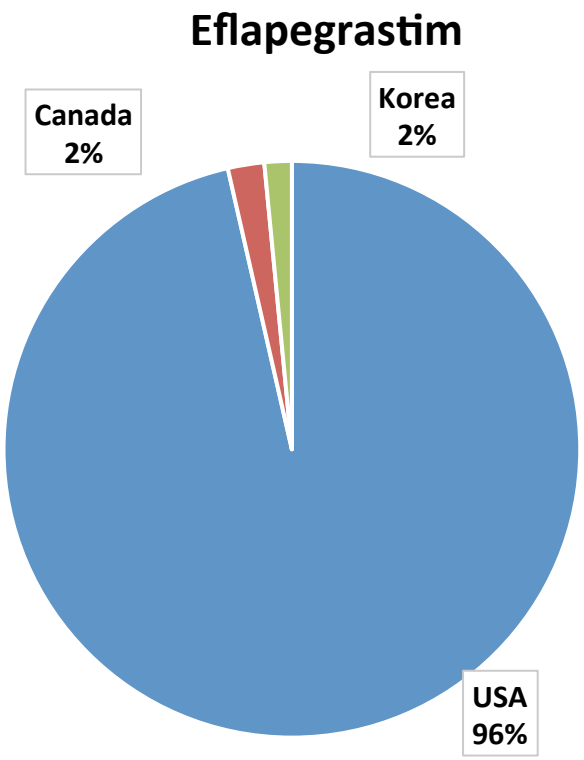


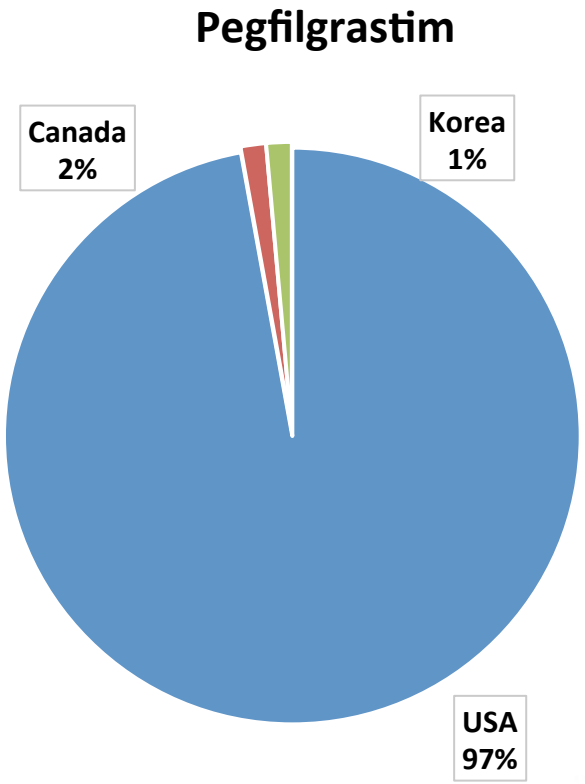


Summary of overall Adverse Events (AE)

AEs by Preferred Term	Eflapegrastim N=197 N (%)	Pegfilgrastim N=208 N (%)
Any AE	192 (97)	203 (98)
Grade 3-4 AE	147 (75)	149 (72)
Serious AE	36 (18)	29 (14)
AE leading to drug discontinuation	9 (5)	11 (5)
AE related to study drug	164 (83)	146 (70)
Grade 3-4 AE related to study drug	37 (19)	23 (11)
AE related to chemotherapy	188 (95)	193 (93)

Enrollment Summary





Summary of Most Common Grade 3-4 Adverse Events (AE >5%)

Adverse Events by Preferred Term	Eflapegrastim N=197 N (%)	Pegfilgrastim N=208 N (%)	p-value
Neutropenia	95 (48)	92 (44)	0.42
Lymphopenia	93 (47)	91 (44)	0.55
Leukopenia	47 (24)	51 (25)	0.91
Neutropenia/Lymphopenia/ Leukopenia	137 (70)	142 (68)	0.83
Anemia	15 (8)	9 (4)	0.21
Febrile Neutropenia	10 (5)	4 (2)	0.10

Duration of Severe Neutropenia in Cycle 1 (ITT Population)

	Eflapegrastim N=196	Pegfilgrastim N=210
DSN (days), n (%) 0 1 2 3	 165 (84) 24 (12) 7 (4) 0 (0)	 159 (76) 32 (15) 17 (8) 2 (1)
N (%) with no severe neutropenia	165 (84.2)	159 (75.7)
Absolute risk reduction in severe neutropenia (%) 95% Confidence Interval*	-8.5 (-16.1, -0.2)	

*95% CI was calculated using Clopper-Pearson method