San Antonio Breast Cancer Symposium® - December 8-12, 2020 • Clinical Trial Registry Numbers: NCT02643420 and NCT02953340
*Eflapegrastim is an investigational drug not approved by the FDA

SPECTRUM PHARMACEUTICALS
Redefining Cancer Care

Pooled Efficacy Analysis from Two Phase 3 Studies in Patients Receiving Eflapegrastim, a Novel, Long-Acting Granulocyte-Colony Stimulating Factor, Following TC for Early-Stage Breast Cancer

Lee S Schwartzberg MD[1], Gajanan Bhat PhD[2], Alvaro Restrepo MD[3], Osama Hlalah MD[4], Inderjit Mehmi MD[5], Yong Wha Moon MD[6], Seungjae Baek MD[7], Shanta Chawla MD[2], Francois Lebel MD[2] and Patrick Wayne Cobb MD[8]

[1]West Cancer Center, Germantown, TN; [2]Spectrum Pharmaceuticals, Inc, Irvine, CA; [3]Texas Oncology PA, McAllen, TX; [4]Bond Clinic PA, Winter Haven, FL; [5]The Angeles Clinic and Research Institute, Los Angeles, CA; [6]Hematology and Oncology, CHA Bundang Medical Center, CHA University, Seongnam, Korea, [7]Hanmi Pharmaceuticals, Seoul, Korea, [8]Frontier Cancer Center, Billings, MT

Background

- Despite the clinical benefit derived from chemotherapy, patients with early-stage breast cancer (ESBC) remain susceptible to developing chemotherapy-induced neutropenia (CIN), a condition which can adversely impact their chemotherapy regimen and compromise long-term outcomes.
- Eflapegrastim (Rolontis®) is a non-biosimilar, long-acting G-CSF, and represents the first myeloid growth factor innovation in more than 15 years.
- Two completed Phase 3, randomized studies (ADVANCE; SPI-GCF-301)[1] and (RECOVER; SPI-GCF-302)[2] involving patients with ESBC treated with TC chemotherapy and eflapegrastim or pegfilgrastim as primary prophylaxis, reported that eflapegrastim and pegfilgrastim exhibited noninferior efficacy and similar safety in the prevention of CIN.

Study Design

- Two identically designed Phase 3 randomized, open label, active-controlled, multicenter studies conducted between 16-Jan-2016 and 06-May-2019 in the USA, Canada, Poland, Hungary, South Korea and India
- Day 1 of each of four 21-day cycles: patients were treated with adjuvant or neo-adjuvant chemotherapy (docetaxel and cyclophosphamide) at the labeled dose (Figure 1)
- Day 2 of each cycle: patients received 1 dose of eflapegrastim 13.2 mg/0.6 mL (3.6 mg G-CSF) or pegfilgrastim (6 mg) 24 (±2hrs) subcutaneously after chemotherapy

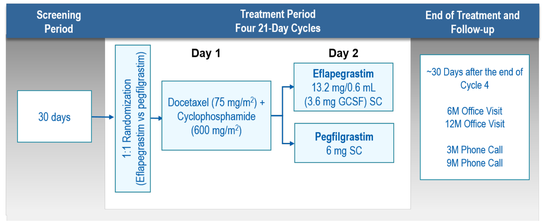
Key Inclusion Criteria

- New diagnosis of histologically confirmed early-stage breast cancer (ESBC) defined as operable Stage I to Stage IIIA breast cancer

Key Exclusion Criteria

- Locally recurrent/metastatic breast cancer
- Previous exposure to G-CSF

Figure 1. Trial Design



Analysis Objectives and Endpoints

- To demonstrate eflapegrastim non-inferiority (NI) to pegfilgrastim as measured by mean duration of severe neutropenia (DSN) in Cycle 1 with a non-inferiority margin of <0.62 days
  - DSN is defined as number of days of severe neutropenia (ANC <0.5 × 10^9/L) from the first occurrence of an ANC below that threshold
- Time-to-ANC recovery, incidence of febrile neutropenia, incidence of neutropenic complications and safety
- Identify patient factors that were associated with the development of severe neutropenia

Statistical Methods

- The current analysis is a post-hoc analysis from the pooled dataset.
- A 2-sided 95% confidence interval (CI) of the difference between the mean DSN of the two arms was calculated using a bootstrap resampling method, with treatment as the only stratification factor.
- Severe neutropenia was evaluated between treatment groups in Cycle 1 using Fisher's exact test at 5% level of significance and was analyzed using multivariate logistic and Cox proportional hazards regression models.
- Univariate and multivariate analyses were conducted to explore potential treatment effects for eflapegrastim vs. pegfilgrastim according to patient subgroups that were categorized by age, weight, and other demographic characteristics.
- Primary analysis population was the intent-to-treat (ITT) which includes all patients that were randomized.

Results

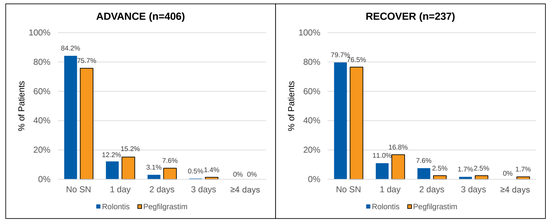
Severe Neutropenia in ADVANCE and RECOVER

- Previously, two Phase 3, randomized studies ADVANCE[1] and RECOVER[2] in patients with ESBC treated with TC chemotherapy, reported that eflapegrastim demonstrated non-inferiority of duration of SN to pegfilgrastim and similar safety in the prevention of CIN (**Table 1**). Non-inferiority of eflapegrastim to pegfilgrastim was demonstrated in all 4 cycles of treatment in both studies.
- The duration of SN was 1 day for most patients who experienced SN (**Figure 2**)
- Eflapegrastim demonstrated relative risk reduction of 34.9% (p=0.034) and 13.6% (p=NS) in ADVANCE and RECOVER studies respectively in the incidence of severe neutropenia as compared to pegfilgrastim (**Table 1**).
- We evaluate severe neutropenia and factors involved in the incidence and time course of severe neutropenia in the pooled dataset of Phase 3 studies.

Table 1. Duration and Incidence of Severe Neutropenia in Phase 3 Studies

	ADVANCE		RECOVER	
	Eflapegrastim N=196	Pegfilgrastim N=210	Eflapegrastim N=118	Pegfilgrastim N=119
DSN (days)				
Mean (SD)	0.20 (0.503)	0.35 (0.683)	0.31 (0.688)	0.39 (0.949)
Median (Range)	0 (0, 3)	0 (0, 3)	0 (0,3)	0 (0,7)
Difference in DSN (days) (eflapegrastim – pegfilgrastim)				
ΔDSN	-0.148		-0.074	
95% Confidence Interval	(-0.264, -0.032)		(-0.292, 0.129)	
Non-inferiority p-value	<0.0001		<0.0001	
Risk Reduction (%)				
Relative Risk Reduction	34.9%		13.6%	
95% Confidence Interval	2.7, 56.4		-40.0, 46.6	
Nominal p-value	0.034		0.554	

Figure 2. Duration of Severe Neutropenia in Cycle 1 in Phase 3 Studies



Patient Demographics

Table 2. Patient Demographics

Characteristic	Pooled ADVANCE and RECOVER		
	Eflapegrastim N=314	Pegfilgrastim N=329	Total N=643
Age, Mean (SD), years	59.2 (11.20)	58.7 (12.11)	58.9 (11.67)
<65 years	192 (61)	208 (63)	400 (62)
≥65 years	122 (39)	121 (37)	243 (38)
Weight, Mean (SD), kg	79.2 (18.46)	79.7 (20.30)	79.4 (19.41)
<75 kg	296 (94)	300 (91)	596 (93)
≥75 kg	18 (6)	29 (9)	47 (7)
Race, n (%)			
White or Caucasian	241 (77)	255 (78)	496 (77)
Black or African American	37 (12)	39 (12)	76 (12)
Asian	29 (9)	25 (8)	54 (8)
Other	7 (2)	10 (3)	17 (3)
ECOG Performance Status, n (%)			
0	239 (76)	237 (72)	476 (74)
1	75 (24)	86 (26)	161 (25)
2	0	6 (2)	6 (1)

Duration of Severe Neutropenia in Cycle 1

- The mean DSN for the Eflapegrastim Arm was 0.24 (±0.581) days compared with a mean DSN of 0.36 (±0.789) days in the Pegfilgrastim Arm (**Table 3**).
- The difference in mean DSN between the Eflapegrastim Arm and the Pegfilgrastim Arm was -0.120 days (95% CI: -0.227, -0.016). Both noninferiority (nominal p<0.0001) and statistical superiority (nominal p=0.029) were demonstrated for the Eflapegrastim Arm compared to the Pegfilgrastim Arm.
- Eflapegrastim treatment was associated with a 27.1% relative risk reduction versus pegfilgrastim in the incidence of SN in cycle 1 (17.5% vs. 24.0%, p = .043).

Table 3. Duration of Severe Neutropenia in Cycle 1 (ITT Population)

Parameter	Duration of Severe Neutropenia in Cycle 1 (days)	
	Eflapegrastim (n=314)	Pegfilgrastim (n=329)
Duration of Severe Neutropenia (days)		
N	314	329
Mean (SD)	0.24 (0.581)	0.36 (0.789)
Median (range)	0 (0, 3)	0 (0, 7)
Difference with Peg	-0.120	
95% CI	-0.227, -0.016	
Non-inferiority p-value	<0.0001	
Superiority p-value	0.029	

Subgroup Analyses

- Both univariate and multivariate analyses including 5 patient subgroups (treatment of eflapegrastim, age <65 years, weight <75 kg, baseline ANC<6.0 × 10^9/L, and US region) were performed. Multivariate analysis showed no stratification significance for any of the above subgroups in the incidence of SN.
- There was no difference in the incidence of SN between eflapegrastim and pegfilgrastim when stratified by age group (<65 years and ≥65 years) in the univariate analysis (**Table 4**).
- When stratified by weight, the incidence of SN was lower in eflapegrastim group of patients ≥75 kg (8.6% vs. 14.1%, p=0.034) indicating that patients with weight ≥75 kg treated with eflapegrastim were less likely to develop severe neutropenia (**Table 4**).

Table 4. Patients with Severe Neutropenia in Cycle 1 (Safety Population)

Variables	Subgroups	Patients with Severe Neutropenia in Cycle 1	
		Eflapegrastim (N=314)	Pegfilgrastim (N=329)
Age, n (%)	**<65 years**	**24 (7.6)**	**38 (11.7)**
	≥65 years	**31 (9.9)**	**41 (12.6)**
Weight, n (%)	**<75 kg**	**28 (8.9)**	**33 (10.1)**
	≥75 kg	**27 (8.6)***	**46 (14.1)**

* p=0.034

Time to ANC Recovery in Cycle 1

- The median Times to ANC Recovery for the patients treated with both eflapegrastim and pegfilgrastim were similar (7 days) **(Table 5)** and the ratio of log Time to ANC Recovery in patients with Cycle 1 severe neutropenia between the two treatments arms was 0.975 (95% CI: 0.94, 1.012; p=0.179).

Table 5. Time to ANC Recovery in Cycle 1 (ITT population)

Parameter	Time to ANC Recovery in Cycle 1 (days)	
	Eflapegrastim (n=314)	Pegfilgrastim (n=329)
N	**55**	**79**
Mean (SD), days	**7.24 (0.607)**	**7.46 (1.107)**
Median (days)	**7.00**	**7.00**

Safety Results

- Febrile neutropenia is defined as an oral temperature >38.3° C (101.0° F) or two consecutive readings of ≥38.0° C (100.4° F) for two hours and an ANC <1.0 × 10^9/L in Cycle 1.
- The incidence of febrile neutropenia in Cycle 1 was 1.6% (n=5) for the patients in the Eflapegrastim arm and 1.8% (n=6) for the patients in the Pegfilgrastim arm, which was not significant.
- The incidence of neutropenic complications was 2.9% (n=9) for the patients treated in the Eflapegrastim Arm and 4.0% (n=13) for the patients in the Pegfilgrastim Arm, which was not significant (p=0.519).
- The safety profiles in general including adverse events were similar between eflapegrastim and pegfilgrastim

Conclusions

- Eflapegrastim showed a lower DSN compared to pegfilgrastim in the pooled dataset of early-stage breast cancer patients who are candidates for chemotherapy.
- Eflapegrastim showed a 27.1% relative risk reduction for the development of SN as compared to pegfilgrastim in Cycle 1.
- Univariate subgroup analyses of SN indicated that eflapegrastim showed risk reduction for patients who weighed ≥75 kg but the difference was not clear in a multivariate stratified analysis.
- Eflapegrastim and pegfilgrastim have a similar safety profile.

Acknowledgements

- We would like to thank all patients and their families
- Both trials were sponsored by Spectrum Pharmaceuticals, Inc.
- Statistical analysis support was provided by Pamela Hsu and Changsheng Wang, PhD at Spectrum Pharmaceuticals, Inc.
- Writing Support was provided by Steven Hasal, PhD and Bram Goldstein, PhD at Spectrum Pharmaceuticals, Inc.

References

1. Schwartzberg LS, Bhat G, Peguero J, Agajanian R, Bharadwaj JS, Restrepo A, et al. Eflapegrastim, a Novel Long-Acting Granulocyte-Colony Stimulating Factor for the Management of Chemotherapy-Induced Neutropenia: Results of a Phase III Trial. The Oncologist. 2020;25(8):e1233-e41.
2. Cobb PW, Moon YW, Mezei K, Lang I, Bhat G, Chawla S, et al. A Comparison of Eflapegrastim to Pegfilgrastim in the Management of Chemotherapy-Induced Neutropenia in Patients with Early-Stage Breast Cancer Undergoing Cytotoxic Chemotherapy (Recover): A Phase 3 Study. Cancer Med. 2020;9(17):6234-43.